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SECTION OF GEOLOGICAL SCIENCES

LUNAR VOLCANIC MECHANISMS*

Jack Green

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"The little we believe we know of what is called the volcanicity of the Moon depends too, from the very nature of the knowledge, on configuration alone."

A. von Humboldt (1851)

It is of interest to inquire if conditions for the evolution of volcanic forms may be different on the moon than on the earth. If most of the major lunar surface features are of an internal origin, what might be suggested as mechanisms intensifying lunar volcanism?

Two forces operative on the moon to a degree not present on earth are tides and gravity (TABLE 1). These forces may trigger regional lunar volcanism. The tidal effects would be those induced by the earth. Tides would be created because the lunar orbit is not a circle; its mean eccentricity is 0.0549. Therefore, at apogee it is 50,000 km. farther from earth than at apogee. From the formula $f = 2g\,M/r^3$ (Russel *et al.*, 1945) where f is the tidal force, g is acceleration in terms of earth's gravity, M is mass in terms of lunar mass units, and R is distance in terms of the minimum earth-moon distance, we can obtain the ratio of tidal forces given in TABLE 2 for apogee and perigee distances today and for the geological past.

F. R. Moulton's (1923, p. 457) value of 20 for the ratio of tidal force on the moon relative to the earth approximates the 13.5:0.7 ratios cited in TABLE 2. The tidal force at perigee of the earth on the moon is 13.5 times greater than that of the moon on the earth; at apogee the ratio is 9.1. The difference in ratios at perigee and apogee is 4.4; therefore if the body tide of the earth produced by the moon is 30 cm. (Gutenberg, 1951, p. 173), then the difference in tide height raised each month on the moon between apogee and perigee is about 1.3 m.

If the lunar apogee-perigee radius were half the present, the tidal force ratios would be increased as shown in TABLE 2 with a tidal difference of 10.5 m. (based on an 8×30 cm. body tide raised on the earth). Arbitrarily retaining a present apogee-perigee radius difference of 50,000 km. for a half-radius earth-moon model, the tide raised on the moon between apogee and perigee could have exceeded 17 m. Because the

*This paper, illustrated with slides, was presented at a meeting of the Section on November 2, 1961.

TABLE 1

FACTORS POSSIBLY INTENSIFYING LUNAR VOLCANISM

Tidal effects in lunar crust
Extensive fracturing of crust
Cyclic pressure release
Generation of magma
Cyclic temperature drop
Onset of magmatic crystallization
Intensification of the second boiling point effect
Explosive pressure rise under crustal plates
Gravity effects in lunar crust
Deeper nucleation of bubbles in magma column
Slower rise of bubbles
Expansion of bubbles during rise
Greater viscosity of magma column top
Enhanced throwout effect during eruption
Rock froths
Greater degree of subsidence in magma column after degassing

TABLE 2

RATIO OF TIDAL FORCES

$f = 2g\frac{M}{r^3}$	Present	Geological Past	
		Half present perigee radius	
	Apogee-perigee distance of 50,000 km.	Apogee-perigee distance of 25,000 km.	Apogee-perigee distance of 50,000 km.
1 $f_{\text{perigee moon on earth}}$	1	8	8
2 $f_{\text{apogee moon on earth}}$	0.7	5.5	3.8
3 $f_{\text{earth on perigee moon}}$	13.5	108	108
4 $f_{\text{earth on apogee moon}}$	9.1	73	51.5
Difference 3-4	4.4	35	56.5
Resulting difference in tide height on moon between apogee and perigee based on a 30 cm. body tide at present on the earth	1.3 m.	10.5 m.	> 17 m.

moon's radius of curvature is almost four times that of the earth, the tendency to fracture would be greater even if the tidal heights mutually raised on the moon and earth were the same. Moreover, the rate at which fracturing would tend to occur at half radius would approach a once-a-week cycle instead of the present monthly cycle.

Tides of the magnitude suggested in TABLE 2 might induce pressure release in the lunar crust in two ways: (1) production of deep-seated fractures, and (2) movement of the base of one lunar crustal block relative to the other. As possible evidence for this tidal activity, the lunar crust is conspicuously fractured (Bülow, 1957). Both the effect of crustal fracturing and displacement of blocks are closely related in time and place. In the first case, a deep open fracture induced by tides would effect immediate pressure release at depth, and molten rock would rise possibly to the surface, assuming conditions of temperature and pressure were correct. In the second case a crustal block, because of density variations or prexisting flotational nonequilibrium conditions, would suddenly yield along border zones of weakness by earth-induced tides to produce a pressure release at the base of the crustal plate in question. Fracturing would produce an immediate pressure release at the base of the crustal plates that would be uncompensated for until the subcrustal material flowed into the low pressure zone.

One aspect of this phenomenon has been discussed by Yoder (1952) where melting has occurred by relief of a tensile stress and by Uffen (1960) where melting has occurred by relief of a compressive stress. The significant difference is that on release of a tensile stress the melting temperature rises to its normal temperature, which may be above the ambient temperature, whereas on relief of a compressive stress the melting temperature decreases to its normal value which may be below the ambient temperature. In both cases local melting may occur. In the case of a pivoted crustal block, the Yoder mechanism of pressure release may be operative in the uptilted portion and the Uffen mechanism may occur in the downtilted portion if relief by fracturing occurs there.

FIGURE 1 is essentially a lunar application of Yoder's concept. On earth we find that the melting curve of basalt has a lower slope than on the moon because of the difference in gravity. If the geothermal gradient in the moon is close to that in the earth, basalt will melt at a shallower depth and at a lower temperature in the moon than in the earth. Because of the steeper lunar melting curve, it will intersect the thermal gradient at a temperature of 1017° C. at 30 km. of depth in contrast to 1117° C. at 43 km. of depth in the earth. However, the assumption of a heat thermal gradient in the moon equal to that in the earth cannot be defended without a better estimate of the lunar heat balance. What is undeniable is the fact that a pressure release per kilometer of overburden to reach the melting point of basalt would be less on the moon than on the earth. As FIGURE 1 indicates for the same rock column thickness – 10 km.

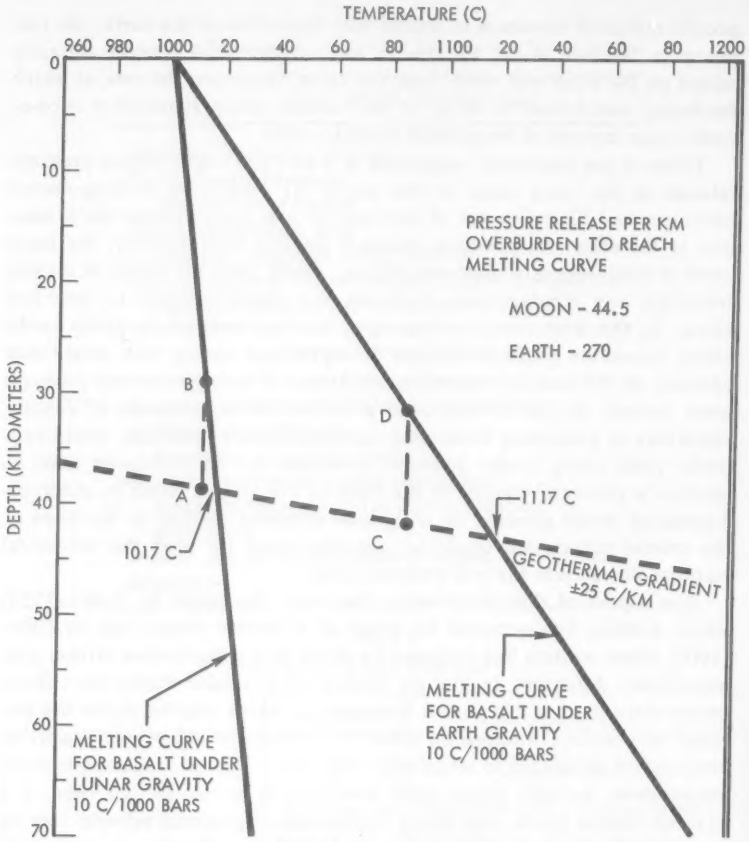


FIGURE 1. Intensification of lunar volcanism

for A-B – a pressure release of 445 bars is required for a rock on any assumed thermal gradient to reach the melting curve. The pressure release in the earth for a rock of the geothermal gradient to reach the melting curve over the same rock column thickness of 10 km. (C-D) is 2700 bars.

In other words, because of the relationship of the melting curves of rocks to the geothermal gradient on the moon, one would need a smaller pressure release per kilometer of overburden to produce a rock melt.

Following Yoder's arguments, assuming a pressure release sufficient to reach 10° C. above the melting curve of basalt, one could melt 3 per cent of a given volume of basalt. The volume increase on melting basalt is 11.2 per cent. On melting a plate 1 km. thick at the base of the lunar crust underlying the crater Ptolemaeus, for example, the basaltic magma

resulting from the 11 per cent volume increase (ca. 30 km.^{3}) would be sufficient to flood the crater floor. The depth to which flooding would occur would depend on one's assumptions on extent, depth, and width of of feeder fractures. Even for an extensive fracture system comprising 50 fractures 10 km. long, 40 km. deep, and 1 m. wide, the floor of Ptolemaeus would be flooded to a depth of 1 m. by the 30 cubic km. suggested.

When and if a magma is produced by pressure release at the base of the lunar crust, a phenomenon known as the second boiling point may occur. This effect is produced when a fluid such as a magma cools and crystallizes. The volatiles that are evolved during this crystallization may reach a critical concentration at a temperature sufficient to cause a rapid rise in pressure.

As Turner and Verhoogen (1951, p. 317-318) point out, the temperature at which the maximum pressure occurs will depend upon the chemical nature of the system and in some cases retrograde boiling will not occur. In these systems, the effect of temperature on the vapor pressure of the volatile component might be greater than the effect due to the increasing concentration of volatiles in the magma. In this case the vapor pressure would fall continuously throughout the temperature range. On the other hand, Turner and Verhoogen continue, the effect of increasing concentration of volatiles – water – might predominate so that the vapor pressure would rise continuously until the whole amount of the nonvolatile component has crystallized.

Nevertheless, as Verhoogen (1949, p. 134) states, conditions obtain where the vapor pressure may and probably does increase. One such system that may occur in nature, as detailed by Morey (1922, p. 224-225), is H_2O - K_2SiO_4 - SiO_2.

Miyamoto (1960, p. 3) invokes the second boiling point effect to account for the evolution of gases from the lunar surface, by cooling of magma within the moon. The gases are assumed by Miyamoto to occupy or to have occupied large underground caverns. While I subscribe to the second boiling point concept with the reservations noted above, I do not endorse the underground cavern concept nor the entrapment of large quantities of gases in such chambers. The depth at which the caverns might occur would be at the depth at which magma would cool. Unless the magma were formed extremely close to the surface, I believe that large openings within the lunar crust would be closed by overburden loading. Furthermore, the second boiling point would tend to promote the generation of fractures that would (1) enhance collapse of such caverns even if they were formed, and (2) permit escape of gases that might collect there. Normal collapse mechanisms observable in the volcanic terrains on earth that attend magma withdrawal at depth are therefore thought to have been operative on the moon.

The tidal effects that would tend to fracture the lunar crust and produce the magmatic processes suggested above would be most effective

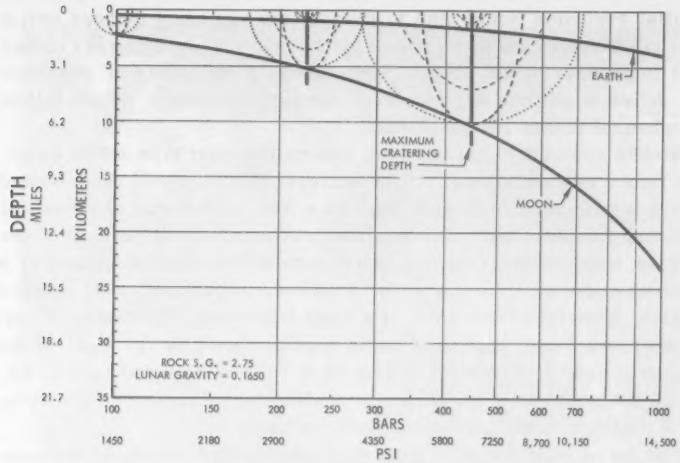
at perigee – a monthly cycle. On earth, pressure differences usually take longer periods to build up. Geosynclines deform under sediment loading over many millions of years; erosional processes reduce pressure on mountain roots over tens of millions of years; and continents "rebound" as glaciers melt over many thousands of years.

The effect of moon-induced tides in triggering regional volcanism on earth over long time periods is practically nil. However, it is important to point out that in isolated cases when the position of a major terrestrial fracture is favorably oriented and when the position of the moon is optimum, tensional forces may be induced to trigger terrestrial volcanism. For example, in the crater chain dominated by Mount Langila on the western end of New Britain Island, each of the four explosive phases of the volcano's activity began during periods close to the maximum lunar declination when the north-south tangential forces of the moon were at a maximum. As the cones in this area are thought to be controlled by a deep-seated east-west fracture, the tangential component of the tractive forces of the moon and sun reach a maximum in positions of extreme declination and produce tension along the fracture. The resulting relief of tension probably aids eruption according to Taylor *et al.* (1957) if conditions within the volcano are close to critical equilibrium.

Perret (1950, p. 129-130) also documents the effect of the moon in initiating volcanic activity at Stromboli, Italy, in 1907

I suggest that tidal influence on the moon by the earth is and has been more intense than the trivial effects noted in promoting activity in terrestrial volcanoes. Many of the effects noted result in recurrence of activity in a volcano already in existence or along fractures of specific orientation. This is probably in contrast to conditions imposed in the lunar crust. I also suggest that conditions for the production of lunar magma have occurred much more frequently in the moon than in the earth over geological time and, therefore, favorable conditions for initiating the second boiling point were enhanced. If the second boiling point does or did occur more frequently on the moon the attendant pressure rise would have given rise to both passive or explosive types of volcanism depending on the depth and disposition of the magma chamber, the type of magma, volatile content, and fracture system associated with it. As implied previously, however, the occurrence of the second boiling point is not a requirement for surface volcanicity; the most important triggering agent is the tidal deformation that would tend to fracture the lunar crust.

Another mechanism independent of periodic generation of magma at depth would be maar type lunar cratering. Maars are produced by relatively near-surface steam effects ranging from a steam-jetting action observed in the formation of a Chilean maar to steam explosions probably responsible for Ugandan maars. Terrestrial features of this type are generally less than 4 km. in diameter. Steam pressures at the critical temperature ranging between 100 to 300 bars are common in volcanic eruptions



STEAM TEMP.	241°C (467°F)		310°C (591°F)		374.4°C (706.1°F)		1200°C (2192°F)	
PRESSURE	34 BARS (490 PSI)		100 BARS (1450 PSI)		222 BARS (3220 PSI)		450 BARS (6520 PSI)	
	DEPTH	VOLUME	DEPTH	VOLUME	DEPTH	VOLUME	DEPTH	VOLUME
EARTH	0.13 KM (420 FT)	0.005 KM^3 0.001 MI^3	0.38 KM (1220 FT)	0.11 KM^3 0.026 MI^3	0.85 KM (2710 FT)	1.3 KM^3 0.28 MI^3	1.67 KM (5480 FT)	9.7 KM^3 2.3 MI^3
MOON	0.78 KM (2560 FT)	1 KM^3 0.24 MI^3	2.3 KM (7400 FT)	25 KM^3 5.7 MI^3	5.0 KM (16,400 FT)	270 KM^3 63 MI^3	10.1 KM (33,200 FT)	2150 KM^3 520 MI^3

FIGURE 2. Relative crater depths and volumes produced by steam pressure.

(Williams, 1954, p. 319) and only rarely reach above 450 bars. The highest value recorded of 569 bars is that for the June 7, 1938, Asama volcano eruption (Minikami, 1942, p. 91). At the critical temperature of water (374.4° C.), the pressure produced is 2.1×10^6 kg./m.^{2} (FIGURE 2). On earth this could lift and subsequently eject a column of rocks some 970 m. thick, but on the moon, because of the lesser gravity (and disregarding the effect of lack of air resistance), the pressure generated by steam at the critical temperature could throw out a column of rock over 5800 m. thick.

The dotted profiles in FIGURE 2 indicate the maximum calculated volume ratio of lunar maar craters to terrestrial ones is 200:1. There are three factors that would tend to reduce this ratio: First, if the steam-jetting activity predominates as a maar-producing process it would simply enlarge a single conduit system albeit from a greater depth on the moon. A deeper and steeper crater would be stoped out there whose initial profile would be within the dotted lines of FIGURE 2, perhaps approximating the heavy dashed line profile.

Second, if the steam explosion mechanism predominates, the inertia of a mass comprising the lunar hemispherical volume over the few seconds

of initial explosion would tend to channel the explosion perhaps into a more bullet-shaped crater as shown by the heavy dashed line in FIGURE 2. No large mass would behave homogeneously and zones of weakness may define a pattern suggestive of cone sheets which do not follow hemispherical planes but are steeper.

Third in contrast to caldera-type craters the maar type crater propogates from a relatively small energy nucleus. The supply of super-heated water to a relatively small area imposes a limit to the size of terrestrial maars. On the moon, an immense quantity of superheated water or steam would be required to produce a crater with 200 times the volume of a terrestrial crater by either the jet or explosion mechanisms – an illogical situation. Slumping of the walls of a lunar maar would theoretically have a steeper and deeper explosion crater profile shown by the light dashed lines in FIGURE 2. Throw-out effects have been disregarded in this discussion but would have a tendency to produce deeper craters on the moon, even if depths of crater nucleation were the same.

In so far as estimating the proportion of maar type craters on the moon to the caldera type, it is interesting to note that the features of polygonalism and internal volcanism are relatively absent from terrestrial maars. In the volcanic field in the Kazinga channel area in southwest Uganda, the outside walls of maars are conspicuously lacking in polygonalism and are flat floored. FIGURE 3 does show border scalloping and features that indicate multiple explosions in the same general area. All of the maars shown have diameters of less than 4 km. On the moon, therefore, one might predict that the large craters, those over 15km., if volcanic, would be of the caldera type, particularly if they contain central mountains. A large proportion of the smaller craters – perhaps those under 15 km. – may be of the maar type.

Gravity Effects

Combined with the suggested tidal effects are the gravity effects (TABLE 1). Under the one-sixth gravity that prevails on the moon, there would be a deeper nucleation and slower rise of bubbles in a lunar magma column. In general, the upper portion of this column would tend to become viscous because of the abstraction of heat from the melt by bubble expansion. On the moon, the lesser gravity causing slower rise of gas bubbles than on earth would permit the growth of larger bubbles over a longer time period permitting a more effective heat extraction in the upper portions of the melt chamber or column. The resulting higher viscosity of this lunar magma "cap" may tend to produce a more violent degree of volcanicity if a rapid pressure buildup were to occur below the more viscous portions of the magma column. Another factor promoting a greater degree of lunar volcanic explosivity is the greater rate of bubble expansion relative to rise which would induce coalescence of bubbles in the magma or lava conduits or flows. If the gas pressure of the bubbles

FIGURE 3. Maars in the Kazinga channel area in southwest Uganda. Scale approximately 1: 32,000. (Photo courtesy of Directorate of Lands and Surveys, Entebbe, Uganda, East Africa).

is high, an explosive Plinean eruption will ensue; if low, a *nuees ardentes* flow of the Pelean variety may occur. The lack of atmosphere would promote a more extensive throw-out of material because of the absence of air resistance. The lesser gravity would also add to the increased throw-out effects. Finally, crater for crater the degassing of a longer bubble entrained magma column on the moon would tend to produce a greater degree of subsidence on the moon than on the earth.

Thermal Sources

The temperature in the moon will probably increase with depth to varying degrees depending on what it is made of and how it was formed. On earth, heat sources is the crust may be a result of: (1) radioactive decay; (2) tidal heat; and (3) "primitive" heat arising from the original compression of the protoplanet; (4) pressure; and (5) crystallization of

rock melts. On earth, factors 1 to 3 appear to be primary heat sources and 4 and 5 are secondary. These parameters may be evaluated for the moon, taking into accounts its lesser gravity and smaller size that qualitatively minimizes items 2 and 3 listed above. The lesser gravity would reduce pressures by one-sixth and the smaller size would have accelerated radiative cooling from the primitive condensation phase.

A minor source of lunar heat would be that of factor 5 or that created by meteoritic impact, not listed above. This leaves items 1 and 2 as major sources of lunar heat. Zotov (1960) believes that tidal heat is one of the dominant heat sources in the earth with the source of energy represented by the moon orbiting at a lesser radius than it now has. A critique of Zotov's hypothesis by Y. Lyustikh and V. Magnitskiy indicates that large uncertainties exist. It is my opinion, however, that the effect may be important in calculating the heat budget of the moon, assuming the moon once rotated as it revolved. Earth tides slowing the lunar period of rotation to a month would have resulted in the dissipation of large amounts of heat that may have contributed to volcanicity in the geological past. However, this assumption may not be necessary to invoke if it can be established that radioactive heating is sufficient to induce volcanicity.

Internal heat produced by the radioactive decay of uranium, thorium, potassium, and rubidium would be at least an order of magnitude greater from volcanic rocks than from stony meteorites as the abundance data in TABLE 3 indicates. One can calculate that a thermally insulated silicic rock with the quantities of the radioactive elements shown will heat up some 40° C. in one million years; a basalt will heat up 6° C. During the same time period, an insulated stony meteorite with the abundances shown would heat up less than 0.5° C. The table also indicates the heat rise per million years in these insulated rock types three billion years ago when potassium was much more abundant. Again, chondrites would heat up a degree or so in contrast to the volcanic rock types. If we were to extrapolate the table back to the period of the origin of the moon, perhaps some 4.5 billion years ago, we could list the now extinct radioactive nuclide iodine 129 of a 17 million year halflife. The presence of this nuclide was established by the discovery of xenon 129 in the Richardton chondrite by Reynolds (1960). Other now extinct radionuclides may have been present when the moon was formed that could have provided additional heat sources for intense defluidization and volcanism during the moon's early history.

The heat balance of the moon has been discussed by Urey (1955, 1956). On the basis of the heat evolved by the rock types noted above, one can say that widely different values for the rate of cooling of the moon can be proposed depending upon the lithology assumed for the lunar crust and mantle. A silicic crust could evolve as much as 100 times as much heat as a chondritic crust. The average heat production of a chondritic moon is 2.3×10^{-7} calories/sq.cm./sec. (Jaeger, 1959). On this basis,

TABLE 3

TEMPERATURE INCREASE IN INSULATED LUNAR MATERIALS

		SILICIC ROCKS (rhyolite-granite clan)			MAFIC ROCKS (basalt-gabbro clan)			CHONDRITIC ROCKS (high and low iron groups)		
			Heat Production per Million Years			Heat Production per Million Years			Heat Production per Million Years	
Element	Annual Rate of Heat Generation ($cal\ g^{-1}$)	Abundance in ppm	Last Million Years	Three Billion Years Ago ($cal\ g^{-1}$)	Abundance in ppm	Last Million Years	Three Billion Years Ago ($cal\ g^{-1}$)	Abundance in ppm	Last Million Years	Three Billion Years Ago ($cal\ g^{-1}$)
Uranium	0.75	4	3.00	7.17	0.5	0.375	1.207	0.01	0.0075	0.0245
Thorium	0.203	20	4.06	4.71	3	0.608	0.704	0.02	0.004	0.0046
Potassium	27×10^{-6}	40,000	1.08	5.16	5000	0.135	0.645	850	0.023	0.110
Rubidium	38.9×10^{-6}	200	0.008		20	0.001		5	0.000	
Samarium	342.5×10^{-6}	6	0.000		2	0.000		1	0.000	
Total			8.1	17.0		1.12	2.56		0.035	0.14
			Temperature Rise (°C) per Million Years			Temperature Rise (°C) per Million Years			Temperature Rise (°C) per Million Years	
			Last Million Years	Three Billion Years Ago		Last Million Years	Three Billion Years Ago		Last Million Years	Three Billion Years Ago
			40.5	85.0		5.6	12.8		0.17 to 0.35	0.7 to 1.40

K^{40} = 0.0119% of K; Rb^{87} = 28% of Rb; Sm^{147} = 15% of Sm

Note: Abundances taken from compilation by Green (1959). Heat capacities for silicic and mafic rocks taken at 0.2. Two heat capacities taken for chondrites: 0.2 and 0.1; true value probably lies in between. Heat production constants taken from Rankama (1954, pp. 119, 305, 306).

and assuming a conductivity of 2×10^4, the subsurface temperature is calculated to be 3° C. Fremlin (1959), however, points out that this calculation must be in error inasmuch as the eruption observed by Kozyrev (1959), if volcanic, could not then have occurred. Thus the assumption that the moon's surface is chondritic is thought to be incorrect because chondrites cannot supply the amount of heat necessary to induce volcanism.

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SECTION OF CHEMICAL SCIENCES

DETERMINATION OF THE LOWER LIMITS FOR THE RATE CONSTANTS OF A HAPTEN-ANTIBODY REACTION BY POLAROGRAPHY*

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Introduction

The most striking feature of antibody-antigen reactions is their specificity, and in this respect they are similar to enzyme-substrate associations.[1] In spite of the many efforts made to understand the detailed mechanism of the latter reactions,[2] the exact nature of the forces and of the conformational requirements underlying the primary step leading to the formation of enzyme-substrate complexes has, as yet, not been established. This is primarily due to the fact that the factors determining this step are usually obscured by fast secondary processes resulting in the chemical modification of the substrate. In contrast, antibody-antigen reactions are simpler, involving only the union of the two reaction partners, and therefore, one might hope to be able to establish the mechanism of these reactions from a study of their kinetics. Moreover, the conclusions derived from such studies might also apply to the mechanism involved in the primary interaction of enzymes with their substrates.

A few studies of the speed of antibody-antigen associations have been reported.[3-9] However, in all of these investigations the antigens used were complex biological macromolecules possessing determinant groups of unknown structure. In addition, the kinetics of the primary step in most of these systems were obscured by secondary reactions leading to the formation of aggregates of different size. To avoid these complications an attempt was made in the present study to investigate the kinetics between well-defined, univalent haptens and their homologous rabbit antibodies. With such systems only the soluble bimolecular and termolecular complexes, AbH and AbH_2, can be formed (where Ab and H represent the antibody and hapten molecules, respectively). Furthermore, on the assumption that the two active sites of an antibody molecule react independently of each other, and neglecting any effects due to the heterogeneity of antibodies,[10] the rate constants of the reactions $Ab + H \rightarrow AbH$ and $AbH + H \rightarrow AbH_2$ may be considered to be identical.

On the basis of the kinetic studies referred to above, it was suspected that these reactions were fast and, therefore, it was decided to

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resort to a sensitive physical method capable of measuring changes in the concentration of the unbound hapten in the micromolar range over short intervals of time. Cathode-ray polarography seemed to satisfy these requirements and was chosen for the present study, particularly since Breyer and Radcliff[11] had previously shown that the extent of the association between protein-azo-hapten conjugates and antibodies homologous to the hapten could be measured by conventional polarographic methods. The hapten employed in the present investigation was *p*-(*p*-aminophenylazo)-phenylarsonic acid (hereafter referred to as R°), the azo group of which is readily reducible at the dropping mercury electrode. To establish the usefulness of cathode-ray polarography for the study of appropriate antibody-hapten reactions, the results obtained by this method were compared with those obtained by equilibrium dialysis, the method commonly used to study these reactions.

Experimental Procedure

Materials. Antibodies to R° were produced by the immunization of rabbits with R°-azo-bovine gamma-globulin conjugates. Gamma-globin fractions containing the antibodies were isolated from pools of antisera according to the method of Marrack *et al.*[12] and were used in all experiments. The compound R°* was purified by crystallization of the hydrochloride in ethanol solution. All solutions used in this study were made up in borate buffer, *p*H 8.0 and $\mu = 0.15$.

Apparatus and methods. The cathode-ray polarograph was similar to that designed by Snowden and Page[13] and was modified to operate in conjunction with an electromechanical device for knocking the mercury drops off the electrode at predetermined intervals of time. For this study, the voltage sweep was made to occur within 0.1 sec. For the kinetic studies measurements were made at one second intervals, and at 5 to 6 sec. intervals in the equilibrium experiments. The results of each measurement were presented on the screen of the cathode-ray tube and could be recorded photographically. Some typical polarographic patterns obtained with an antibody solution in the absence and presence of R° are shown in FIGURE 1. The height of the peak in the pattern on the right corresponds to the amount of hapten available for reduction. The peak height for a given quiescent solution containing the antibody and the hapten R° varied within less than ± 2 per cent of the average value obtained in successive readings. However, when the solutions were being stirred, the variations in peak height were as large as ± 8 per cent.

The polarographic cell consisted of a specimen vial (13 mm. i.d. and 60 mm. high) which was immersed in a thermostat maintained at 20 ± 0.1° C. Volumes of 1 to 2 ml. of the antibody solution (about 10^{-5} *M* with respect to antibody sites) were used for each experiment. The nonpolariz-

*Obtained from Aldrich and Co., Milwaukee, Wis.

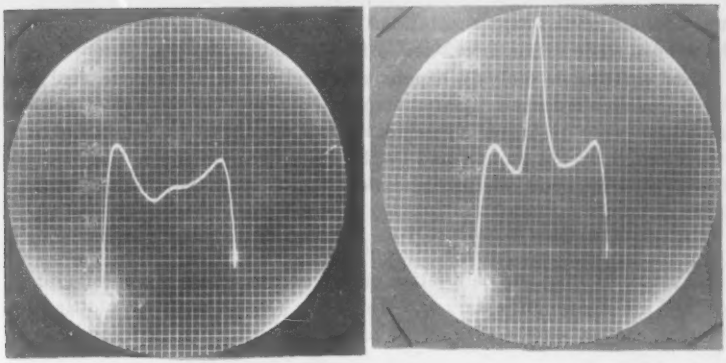

FIGURE 1. Polarographic patterns for an antibody solution in the absence (*left*) and in the presence (*right*) of the reducible hapten, *p*-(*p*-aminophenylazo)-phenylarsonic acid. Reduction occurs at a potential of about -0.5 v with respect to the saturated calomel electrode.

able anode was a silver wire encased in a polyethylene tube (1.5 mm. i.d.) filled with 25 per cent KCl, and was separated from the protein solution by an agar gel plug. Protein solutions were deoxygenated in the cell by passing a gentle stream of purified nitrogen over their surface for 10 to 15 min. and by simultaneously stirring with a magnetic stirrer. During the course of an experiment, a very slow stream of nitrogen was passed over the solution. The deoxygenated hapten solutions were added in microliter quantities to the antibody sample with an "Agla" micrometer syringe.*

For equilibrium studies binding curves were obtained by adding a 10^{-3} M solution of R° to the antibody solution in increments of microliters and measuring the peak height 30 to 60 sec. after mixing, at which time the solutions had become quiescent. Calibration curves for the peak height as a function of the concentration of R° were obtained with solutions of R° in the presence of the antibody and of the nonreducible hapten, benzenearsonic acid. The latter compound was added in about a 2000-fold excess with respect to the concentration of antibody sites and, when used in such high concentrations, was shown to be an effective inhibitor of the reaction between R° and the homologous antibodies. Using this procedure it was possible to obtain calibration curves under conditions where only a negligible amount of the reducible hapten, not larger than 2 per cent, was specifically bound by the antibodies.

In experiments intended for the determination of the rates of hapten-antibody interactions, the hapten solutions were added to the antibody solution, which was continuously being stirred. Measurements of the peak heights were made at intervals of one second as soon as possible after

*Manufactured by Burroughs Wellcome and Co., London, England.

the addition of the hapten solutions. The first reading was estimated to have been made within 1 to 2 sec. after the addition of the hapten.

For equilibrium dialysis experiments, cells similar to those designed by Karush[10] were used. Control experiments with normal rabbit gamma-globulins were performed to determine the amount of hapten bound non-specifically by the protein and by the cellulose membrane. The concentrations of unbound hapten were determined spectrophotometrically at 387 mμ.

Results and Discussion

Typical binding and calibration curves obtained with the polarographic method are shown in FIGURE 2. The peak heights used for plotting the binding curves were measured 30 to 60 sec. after the addition of each

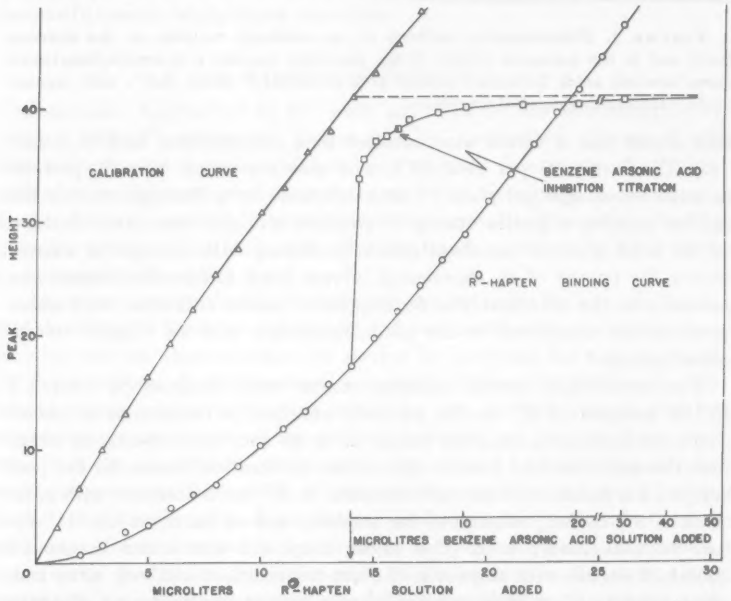

FIGURE 2. The upper line represents the calibration curve for the reducible hapten R° obtained with the antibody solution in the presence of an excess of the nonreducible inhibitor, benzenearsonic acid. The lower continuous line represents the binding curve for R° obtained in the absence of the inhibitor.

increment of the hapten solution. They remained constant within the experimental error of ± 2 per cent and, therefore, may be considered to represent equilibrium values. The precision of the experimental procedure employed was demonstrated by the fact that the various curves obtained from duplicate experiments were closely superimposable. The concentrations of the free and bound hapten calculated from the polarographic

data, or determined spectrophotometrically from equilibrium dialysis experiments, were used in conjunction with the equation[14]*

$$\frac{1}{b} = \frac{1}{c[Ab]K} + \frac{1}{[Ab]}$$

for the calculation of the concentration of the antibody sites, $[Ab]$, and of the intrinsic equilibrium constant, K. In this equation b and c represent the concentrations of the bound and free hapten, respectively.

An "inhibition-titration" curve obtained by the addition of portions of a 0.5 *M* solution of benzenearsonic acid to an equilibrated solution of antibody and R° is also shown in FIGURE 2. This curve represents the amounts of the reducible hapten R° replaced at the antibody site by benzenearsonic acid on the addition of increasing amounts of this nonreducible hapten. As can be seen, the amount of the reducible hapten bound decreased on increasing the concentration of benzenearsonic acid. With the highest concentrations of benzenearsonic acid used, the peak height due to R° reached the value corresponding to that given by the solutions employed for obtaining the calibration curve. These results support the view that antibody-hapten reactions are reversible.

The plots for the polarographic and equilibrium dialysis data obtained from parallel experiments are represented in FIGURE 3. As can be seen

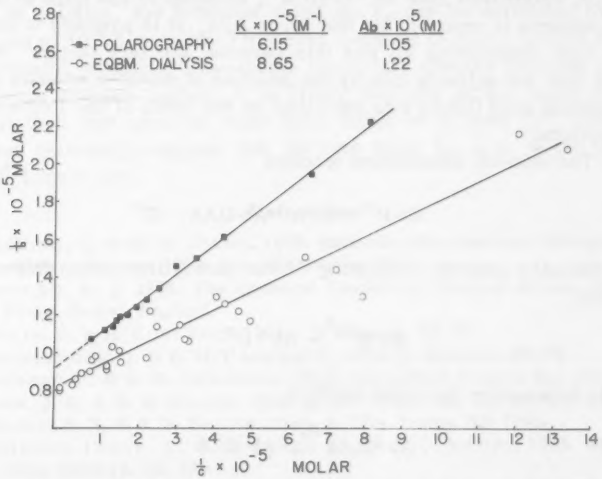

FIGURE 3. Comparison of the data for the extent of binding obtained by polarography and equilibrium dialysis.

*This equation is only applicable to systems in which all of the antibodies have the same affinity for the hapten. The justification for using this equation is that no obvious heterogeneity was detected with the antibody preparation used in the experiments reported here.

in this figure, both the intrinsic equilibrium constant and the concentration of antibody sites calculated from the polarographic experiments were somewhat lower than the corresponding values computed from the equilibrium dialysis experiments. In spite of the discrepancy between the results obtained by the two methods,* it is evident that the polarographic method is capable of measuring the specific binding between the antibody and hapten. Therefore, it was felt that it was justifiable to use this method in kinetic experiments.

In experiments designed to study the rate of the forward step in the reaction

$$\mathrm{Ab} + \mathrm{R}^{\circ} \underset{k_r}{\overset{k_f}{\rightleftharpoons}} \mathrm{Ab}\text{-}\mathrm{R}^{\circ} \qquad (1)$$

an aliquot of R° was rapidly added to the antibody solution and the peak height was observed. The final concentrations of both antibody and hapten were about 10^{-5} *M* in these experiments. After the time of mixing, that is, after 1 to 2 sec., there was no detectable trend in the peak height with time. Thus, within experimental error, the association reaction between antibody and hapten reached completion within this time interval and, therefore, the rate constant, k_f, could not be evaluated directly. However, since the intrinsic equilibrium constant for the antibody-hapten reaction, determined here as $\sim 10^{6}\mathrm{M}^{-1}$, is equal to the ratio of the two rate constants in reaction (1), that is, to k_f/k_r, it is possible to evaluate k_f by first determining k_r. For this purpose, the fact that R° was released from the antibody site by the addition of suitable amounts of benzenearsonic acid (BAA) was exploited on the basis of the following two assumptions:

(1) The over-all substitution reaction

$$\mathrm{Ab}\text{-}\mathrm{R}^{\circ} + \mathrm{BAA} \rightarrow \mathrm{Ab}\text{-}\mathrm{BAA} + \mathrm{R}^{\circ}$$

is a two-step process consisting of the slow, first-order, dissociation reaction

$$\mathrm{Ab}\text{-}\mathrm{R}^{\circ} \overset{k_r}{\rightarrow} \mathrm{Ab} + \mathrm{R}^{\circ} \qquad (1')$$

that is followed by the rapid reaction

$$\mathrm{Ab} + \mathrm{BAA} \overset{k_f'}{\rightarrow} \mathrm{Ab}\text{-}\mathrm{BAA} \qquad (2)$$

(2) The rate constants for the reaction between the antibody molecules and R° on the one hand, and BAA on the other, are of the same order of magnitude (that is, $k_f \approx k_f'$).

*This discrepancy might be due to the reduction or to the dissociation of some of the antibody-R° complexes at the electrode surface.

If these assumptions are correct, then, on the addition of sufficiently large amounts of BAA to an equilibrated solution of antibody and R°, the increase in peak height with time would represent the rate of the dissociation step (1'). In accordance with the above scheme, experiments to determine the value of k_r were performed by adding microliter volumes of a 0.5 *M* solution of BAA to solutions of antibody and R°. The final ratios of BAA to R° used varied from 25 to 1000. In each case the peak height due to R° increased within the time necessary to make the first observation after the addition of BAA, and, within experimental error, further changes in its value could not be detected for periods of time as long as half an hour. Thus, the dissociation reaction, like the association process, was completed within 1 to 2 sec.

Although the dissociation reaction was too rapid for the precise determination of its rate, a lower limit for k_r could be calculated with the aid of the standard expression, $k = (\frac{1}{t}) \ell n (\frac{a}{a-x})$. If t is taken as 1 sec., it follows that k_r must be larger than 1 sec.$^{-1}$. Using this estimate together with the value for the intrinsic equilibrium constant, the minimum value for k_f was calculated as 10^6 ℓ/mole/sec. It is interesting to note that this value for k_f compares favorably with the rate constants determined for some catalase-peroxide associations.[15] and for some protein-dye interactions studied recently with the temperature-jump method.[16] *

On the basis of the theory of diffusion-controlled, bimolecular reactions in solution, the maximum value for k_f can be estimated to be of the order of 10^{10} ℓ/mole/sec. However, because of steric factors and the electrostatic repulsion between the negatively charged antibody and the negatively charged hapten, it is likely that the actual value of k_f is smaller than this maximum value by a factor of at least 10^2. Therefore, one may reasonably suggest that the true value for k_f is of the order of 10^6-10^8 1/mole/sec.

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DIVISION OF ANTHROPOLOGY

A NEW LOOK AT THE EVOLUTION OF THE PRIMATES*

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I propose to discuss and describe some of the general trends that I think we can attribute to that personally most interesting of the orders of Mammals, the Primates. I base these generalizations on the work I have been doing in certain specific areas and upon some extremely clever work by some of my colleagues. There are four principal areas from which I shall draw material: (1) a study of Primate chromosomes, both number and karyotype; (2) a study of the hemoglobins and those serum proteins that are controlled by precisely known genetic mechanisms; (3) recent work on the comparative behavior of various Primates; and (4) general comparisons among various mammals.

Why a new look at the Primates? Anthropologists and their associates have been worrying about the Primates for generations. One would expect that a truly worthwhile body of information would be on hand. Unfortunately, it is difficult to decide whether this is the case or not. Problems of nomenclature, anthroprocentric approaches, and confusion in descriptions of the various Primates have muddles research. It has been difficult to make efficient use of the data that have been collected. Even now we find it is not possible to correlate our data from lemur chromosomes and hemoglobines, for example, with the various descriptions of the animals in the literature. Our data simply do not allow for the classifications made in the past.

Another important reason for looking anew at the Primates and their evolution is the invalidity of a commonly accepted point of view about the general nature of Primate evolution. We read in many elementary texts in zoology and anthropology that the Primates are a primitive, unspecialized, generalized order with no unique trends obvious in their development. I overstate this view perhaps, but I do so with intent. I consider this to be a most reprehensible block to clear thought about evolution in this order. This view can be attributed originally, perhaps, to Earnest A. Hooton. However, the erroneous implications and connotations which this view has developed are most decidedly not his responsibility. For Hooton, I think, this was an heuristic device in order to throw particular trends into dramatic highlight. It has become, however, a slogan – man and the Primates are primitive and generalized and this primitiveness and generality are the reasons for their great adaptability. My objection may be largely on semantic grounds. Nevertheless, to emphasize that pentadactyly and relatively primitive prehensility indicate man and his fellow Primates are primitive and

*This paper, illustrated with slides, was presented at a meeting of the Division on October 23, 1961.

unspecialized is to express a most inadequate view of what evolution is all about.

The development of simple techniques for the culture of mammalian cells has made possible rapid advances in the study of chromosomes and karyotypes of a large variety of animals. The classic diploid number of man, for example, was held to be 48. In the past 5 years it has become quite clear that this number is 46, and deviations from it are usually found in individuals with serious abnormalities. One of the most startling and suggestive aspects of the recent work on human chromosomes, in cultures of skin and peripheral blood, is the relation that apparently exists between aberrations in either the number or the morphology of chromosomes and certain severe congenital disorders.

I shall review, by taxonomic categories, some of the results of the most recent work on Primate chromosomes. *Tupaia glis* and *Urogale everetti* of the Tupaiioidea, the Malayan and Philippine tree shrews, respectively, have been studied. Chromosome counts indicate some considerable difference between these two animals, the former has a diploid number of 60, the latter 44. Since we believe that the Tupaiioidea are directly derived from the Insectivora, it is likely that this variability may be part of their heritage, since the Insectivora show much variation.

Perhaps the most interesting phenomen we have run into in our cytological studies is the great variability of the chromosmes among the Madagascar lemurs. Their numbers range from $2n = 44$ to $2n = 66$, and we have yet to study any of the Indridae, Daubentonidae, or Cheirogalinae. The variability we find in these animals may be related to the ecological variaction that seems to have been true of the Island of Madagascar. Rand's study[1] of the birds of this island leads one to believe that the various pluvial periods isolated a number of ecozones on the island and caused a great diversity among the birds. A similar diversity is apparent among lemurs. The implication of the demonstration by Chu[2] of various karyotypes and numbers of Lemur chromosomes are too special to be discussed in this general paper, but one comment is worth making: it is likely that Milne-Edwards and Grandidier[3] were entirely correct in their original classification of lemurs, while Schwarz[4] and his predecessor Fosyth-Major[5] were completely mistaken.

The *Lorisformes* show only one spectacular difference in chromosomes, which leads to some new ideas about their classification. The small *Galago senegalensis* has a diploid number of 38, while the large *G. crassicaudatus* has 60. This difference is reflected in the histochemistry and cytomorphology of the skin (William L. Montagna, private communication). Our work on the serum proteins and hemoglobins also indicates major differences between these two.

Among the Cercopithecoidea the most interesting feature is the magic number 6. At present the chromosome numbers range from $2n = 42$ to $2n = 72$. All of the intermediate numbers differ from the preceding and suc-

ceeding number by 6 chromosomes. Thus the numbers go 42, 48, 54, 60, 66, 72. The meaning of this progression is not clear yet, and it is the object of considerable study at present. It is true that not all the Cercopithecoidea fit this progression, but the genera *Papio*, *Macaca*, and *Cercopithecus* do. The presumption today is that the genus *Papio* is the most advanced, while *Cercopithecus* is the least.

The great apes have several chromosome numbers, and variations in karyotype. Since the data are not published yet, it would be premature to discuss them in detail here. Suffice to say, there are problems in relating the details of the ape karyotypes to those of man, although some striking resemblances as well as differences exist.

It is apparent that no hybrid exists, or probably occurs, within Primates when the animals involved have different chromosome numbers. A close examination of the literature indicates that no true interchromosome hybrid stands up to close investigation, and those cases of intergeneric or interspecific hybridization that can be verified were between animals with identical chromosome numbers. That evolution of the chromosomes has not ceased is shown by the variations which we see in man. Whether similar variations occur in the infrahuman Primates has to be demonstrated. The XO and XXY of the mouse[6] and the XXY of the tortoise shell cat[7] indicate that chromosomal variations continue to occur in mammals.

The second major topic I propose to discuss concerns the hemoglobins and serum proteins. The most significant discovery we have made in analyzing the hemoglobins of the Primates is that there is a distinct difference between the respiratory pigment of the prosimians and that of the Anthropoidea. The hemoglobin of every adult prosimian we have tested has a major portion of it in an alkali-resistant form. In man, from whom most of our knowledge of the hemoglobin molecule comes, the alkali-resistant pigment is strictly a fetal pigment. This should not, I hope, be read as implying that the prosimian alkali-resistant hemoglobin is the persistence of a fetal character. The structure of this alkali-resistant prosimian hemoglobin is not presently known. However, the fact that all adult pigment exists in two forms is significant. We can separate at least two hemoglobins from each of these animals by starch-gel electrophoresis.

Several things are noteworthy about our data. First, the insectivores (*Elephantulus sp.* for example) studied have an insignificant amount of the alkali-resistant pigment. Second, the small galago had a very low amount, as did *Tupaia*. The lemurs seem to have the greatest amount. The level of this alkali-resistant pigment is very high in the fetal macaque, but not in adult macaques. The hemoglobin from two 90-day fetuses, normal term 168 days, contained up to 85 per cent alkali-resistant hemoglobin. The 14-day-old macaque tested had about 50 per cent while adults had none. This parallels the situation for man. In addition, no alkali-resistant pigment has been found among the juveniles or adults of any of our Cercopithecoidea. Details of the structure of hemoglobin may clarify the nature

of this alkali-resistant pigment. In man, fetal hemoglobin has two polypeptide chains that are sufficiently different from the analogous two in normal adult A hemoglobin to warrant labeling them "gamma" instead of "beta" chains.

As far as we know today, the alkali-resistant property lies in this gamma chain. Ingram[8] points out that it is not yet possible to attribute the alkali-resistant property to any characteristic of the molecule. In other vertebrate orders the hemoglobin, or other respiratory pigment, appears in different forms consequent to differend demands made upon the organism. It is not beyond reasonable speculation to suggest that the extremely active, arboreal prosimians may find it useful to have some hemoglobin in a structural form that releases oxygen more rapidly than the normal A form. Conversely, it may be that the more complex nervous systems of the Anthropoidea require such a rich and constant oxygen supply that deviations from the normal A structure are disadvantageous, unless special circumstances occur. These speculations are, I warn you, quite unproved.

A subsidiary finding in our laboratory may support this view. After scanning hundreds of macaque hemoglobins we felt this was one of the dullest of the animals with which to work. We never found, upon electrophoresis, more than the two "normal" bands that have been reported by others. Usually we found no variation. This was confirmed in another laboratory (R. Owen, private communication). However, Gertrude van Wagenen presented us with some blood from her inbred macaque colony. Samples taken from a highly inbred sibship proved to have multiple hemoglobin bands when tested by starch-gel electrophoresis. A similar discovery was made among some samples from a moderately inbred South African baboon colony. The implication is, I think, that animals which must survive in the fierce life of the jungle or the plains cannot survive if the hemoglobin is not all or largely in the efficient A form. However, in protected groups, such as the inbred colonies referred to, the mutations may persist.

The serum proteins of man and other mammals have recently been divided into a number of genetically controlled systems. The most striking are the serum transferrins, iron-binding proteins in the beta-globulin fraction. Starch-gel electrophoresis produces very refined distinctions among various bands of these transferrins. Furthermore, the starch-gel acts as a molecular sieve[9] and larger molecules move more slowly in the system than do small ones. This enables us to distinguish the various transferrins as molecules of different size as well as of different charge. The data we have, in summary, indicate that the transferrins of the Primates increase in size, that is, decrease in mobility in starch-gels with increase in complexity of the animal. The prosimian transferrins are generally quite rapid moving, so are those of the Cercopithecoidea. Those of the apes and man, on the other hand, are quite slow.

To summarize this section of my talk, the evidence from our biochemical genetic work is that there is a distinct break between *Prosimii* and Anthropoidea when considering the nature of the hemoglobin. Furthermore, there

seems to be a correlative change in certain serum proteins as one goes from the bottom to the top of the phylogenitic tree. There is, it might be well to note, a similar increase in size in the hemoglobin molecule from prosimian to man.

Item three concerns the nature of the social behavior of these animals. In summary, it is legitimate to point out, from the evidence we have, that behavior which tends to make social groupings more cohesive among the Primates is emphasized by natural selection. Along with this, or perhaps fundamental to it, is the increase in complexity, size, and efficiency of the nervous system. One most interesting thing about the trend of sociality among the Primates is the fact that there is a continually lengthening period of gestation and period of dependence of infant upon mother. Among most prosimians this period is relatively brief. *Galagos*, for example, are left behind by their mothers in nests and hollow trees almost immediately after birth. Our evidence, of course, depends upon our observation of maternal behavior among our colonial *Galagos*. The lemurs, on the other hand, seem to show, at least among "higher" lemurs, a great deal of dependence. One baby lemur in our colony clung to its mother with great tenacity for the first three weeks of life. For at least one month thereafter she would not desert her mother surrogate (an old fur glove) for more than 30 or 40 sec. At 2 months, she finally was able to leave it for longer and longer periods and finally at 2½ to 3 months, we were able to remove the surrogate. Washburn and DeVore[10] report lengthy periods of mother-infant relationship among baboons, and the period of infantile dependence in man is great.

The trend against multiple births is certainly true of all Primates, and that only the smallest and probable most primitive Prosimians, such as *Microcebus*, produce multiple births (twins) regularly. Unfortunately, recently one of our *Galagos*, the large variety, produced triplets, and all six of her mammary glands were fully functional. There is nothing vestigial about the six nipples during such a period of crisis.

Calls, grooming behavior, and other social responses[11] are of great importance and are apparently increasingly complex as social structure increases in complexity. At least much of the social cement of a Primates group, whether it be lemur or baboon or ape, is grooming. The amount of grooming behavior is related to some extent to the estrus cycle – much more grooming occurs between pairs of *Galagos* when females are in estrus and such grooming is of course, common during the infantile dependency period. Among lemurs grooming behavior is relatively complex and important. The intensity and diversity of such grooming indicates, as does the behavior of the mother and infant, that some lemurs have achieved a social level equivalent to that of the old world monkeys.

Some extremely clever studies by Alison Bishop suggest that some of the increase, if not all, in manipulative ability in the higher Primates is very likely due to the use of accurate fine movements of the hand in grooming, which have not appeared, except in a rudimentary sense in lemurs. The specialization of the incisors of lemurs for grooming may well have

resulted in this lack of emphasis on fine movements and eye-hand coordination in these animals.

Finally, I propose to point out certain general features of the Primates, as compared with other animals, which have evolutionary implications. The life span of most Primates is much longer than other mammals, and the trend throughout the order is for increased longevity. The tiny *Microcebus* (average adult male weight is about 90 g., females weigh close to 120 g.) has a demonstrated life span of at least 6 years. (F. Bourliere, private communication). The tarsier has been recorded dying after 12 years in a zoo. Lemurs have lived for at least 20 years, and at least one female macaque is known to be 33 years old with only the first sign of irregular menses now appearing. Although one can always cite the elephant to show that other mammals also live a long time, it is the general trend that is impressive.

The complex nervous system of Primates requires not only efficiently produced metabolic oxygen, but also a more complex diet than that of more primitive mammals. The energy binding and using dimensions, to use a currently fashionable expression, of Primates are more intense and efficient than that of other mammals. Diet requirements indicate that metabolism is at a higher energy level than that of other animals. The psychological needs, if such they be, seem more intense and developed, as a whole, than those of other orders of animals. Solitary chimps are said to pine away, and we have noticed the intensity with which lemurs react to reunion with their fellows after a period of isolation.

This brings us to a final review of what I have said. First, the Primates are, I claim, a very complex, advanced, and special evolutionary development. This special advanced complexity is best symbolized by the advanced nervous system of the members of the order. Second, the generalized primitive characteristics are merely those of general morphology. Once a sufficiently decent body form developed, and the great event of efficient prehensility occured, the action of selection may be seen to focus upon those neuromuscular events that improve eye-hand coordination, visual acuity and memory, and eventually erect bipedalism and the mutations that led to symbolic behavior. Third, the information transmitting mechanism, the genetic material, the chromosomes, must, in the complex, delicately balanced metabolic machine of Primates, be in practically perfect balance if reproduction is to occur. This is our present explanation for the apparent absence of hybrids between Primates of different chromosome numbers. We note that chromosomal evolution can still occur, witness the trisomy and and translocations of man, but that presently recognized variations in the chromosome complement lead to serious disabilities. Fourth, the evidence we have gathered from our study of the hemoglobin of these animals shows that there is a large difference between the *Prosimii* and the Anthropoidea. We presently attribute this difference to the oxygen needs of these animals, although this is strictly a speculation. A similar explanation may hold for

the progressively differentiating serum transferrins of the Primates. Finally, the behavior of Primates reflects the increasing complexity of the nervous system. Certain aspects of the social complexes and the interindividual actions of these animals clearly have proved to be selectively advantageous. Each of these advances in behavioral complexity and social sophistication may be seen as the consequence of a development in the nervous system.

A final note of caution is in order. Almost everything that I have projected from the data we have in our laboratories and that I have culled from my colleagues may be but the very faintest outline of a completely "new look" at the evolution of Primates, so great is our ignorance of our own mammalian order.

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DIVISION OF MICROBIOLOGY

PROBLEMS OF FIXATION AND STAINING IN MICROBIAL CYTOLOGY*

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In securing preparations of meaningful cytological delicacy, particularly of the smaller microorganisms, the avoidance of artifacts is inevitably a more exacting requirement than is frequently the case with large, well-differentiated tissue cells. The problems encountered in preserving structure in microorganisms in a form closely approximating that prevailing in the living cell are severe in morphological, and more so in cytochemical studies at the levels of both the light and electron microscopes. These difficulties are attributable largely to the two special properties of microbial cells which, among others, distinguish them from higher cell types – diminutive cell sizes and relative paucity of total concentration of cell components – and are a reflection of their place in evolution. They are a reminder of the care that must be exercised in interpreting microbial cytology and in seeking analogies with structural components of advanced cell types. In the smaller microorganisms, limitations in light microscopical resolution preclude accurate descriptions, counts, or behavioral observation of intracellular constituents, particularly in studies of their nuclei. Low concentrations of such components as DNA, enzymes, and sometimes of polysaccharides in wall layers, are liable to prevent spatially accurate localizations with the same facility, positiveness or ease of microscopical visualization possible with most cytochemical reactions performed on higher cell types. The literature of microbial cytology is replete with statements as to the difficulties experienced in obtaining satisfactory preparations for definitive descriptions of detail in internal morphology or chemical identification of cellular components. The sharply divergent and polemical views arising from technical and observational problems are a measure of the uncertainties in interpreting material studied by the usual methods of fixation and staining.

An extensive analysis of the various technical factors that have yielded discrepant cytological conclusions has been made in a recent critical review (Mundkur, 1962). For the purpose of this paper, therefore, I confine attention to only a few selected examples of problems encountered by the microbial cytologist; and, by a comparison of photomicrographs and electronmicrographs of conventionally processed material with that obtained by freezing-drying and specific staining, to indicate the potential of improved techniques.

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As an example of observational difficulty may be mentioned the very weak coloration (consistent with low DNA content) shown by nuclei of frozen-dried yeast after procedures carefully designed to yield a high degree of Feulgen specificity (Mundkur, 1954). On the other hand, weak nuclear coloration may be considerably enhanced by such devices as the use of fixatives containing chromates, mercuric salts, formaldehyde, and picric acid, or by the use of non-Schiff staining solutions such as Giemsa or thionin or azure A. In all of these cases the gain in color intensity is far greater than might be expected on the known prevalence of low quantities of nuclear DNA in yeast. Thus, while the unnaturally augmented colorations may be pleasing to the observer, it seems doubtful that a truly selective localization of this component and a precise estimate of the internal structure of the nucleus were achieved. An explanation for the augmented Feulgen color may properly be ascribed to the staining of aldehyde groups released by oxidation from non-DNA moieties by the fixing fluid or, in the case of non-Schiff type stains, a coloration of DNA as well as of substrate other than DNA. Indeed, with such solutions as Giemsa, which comprise mixtures of dyes producing metachromasy, both the yeast nucleus and cytoplasm are stained simultaneously, and the recognition of the nucleus is achievable only through prior removal of cytoplasmic basophilia by acid extraction or ribonuclease digestion; it seems doubtful, therefore, that the effects are strictly analogous to those yielded by Feulgen staining performed after freezing and drying and adequate postfixation with, for example, alcohol vapor.

Enhanced color intensifies, rather than faithfully reflecting the disposition of nuclear DNA, are attributable to such effects as oxidation, reductions, and cross-linking of radicals, or to other deleterious effects of fluid fixation obscuring both specific identification and spatial localization of chromatin.

An additional example at the light microscopical level of the reduced usefulness of fluid fixatives is provided by the polysaccharidic components of yeast. The traditional use of Lugol's iodine solution as a stain for glycogen may be cited as an illustration. In addition to its capacity for staining several substances unrelated to glycogen, such as various proteins and mucoproteins the entry of Lugol's solution in the cell is accompanied by severe displacements of glycogen, resulting from diffusion gradients within the protoplasm. The ensuing disturbance of glycogen from its normally particulate distribution results in its aggregation and dense clumping along with other stainable substances. If, however, "streaming" or diffusion artifacts of this nature are prevented by freezing and drying methods and, in addition, specific staining for polysaccharides with the periodate-Schiff reaction is employed, the immobilized glycogen is seen to be uniformly disposed as particles rather than as clumps in the cytoplasm. Furthermore, polysaccharidic yeast cell walls, the layers of which are of irresolvable thicknesses in sections examined with the

light microscope, can be selectively localized in the electron microscope with the periodate-Schiff reaction following freezing-drying. A feature particularly helpful in these studies is the applicability of specific enzyme and other controls after freezing-drying, to verify the nature of a group of specifically stainable polysaccharides. It has been possible with these means not only to identify cytochemically but also to visualize morphologically with the electron microscope elementary particles (molecules) of glycogen measuring about 200 Å, the 1:4 linked glycoside mannan, the 1:3 glucopyranoside glucan, acetyl glucosamine, as well as an hitherto unknown and unidentified polysaccharidic component of bud scar plugs (Mundkur, 1960).

The limitations intrinsic to the application of many of the usual procedures involving fluid fixation and staining in microbiology are, in effect, not different categorically from those well known in higher cell types. They include artifacts of morphology such as aggregation, precipitation, dissolution, or other changes often resulting in marked deviations from the morphology of the living cell; they include also the production through chemical interactions, such effects as the formation of previously absent compounds, or losses or total destruction of enzymes and other cellular components. Owing to the difficulties in observation of small cells like yeast, bacteria, or certain algae and protozoa, these effects may cloud a correct interpretation of microbial structure far more severely than in studies of large cells with well-differentiated spindles, chromosomes, mitochondria or other clearly defined inclusions. Reductions in total cell and nuclear volumes following fixation with conventional agencies such as reported from work on *Helix* primary spermatocytes (Ross, 1953) are well known in cytology. Shrinkage of microorganisms ensuing from conventional procedures of treatment may be severe enough to nullify interpretations of internal detail, particularly of the nucleus of many small microorganisms, even though the shrinkage in total cell volume may not superficially be striking under the microscope. The air-drying or heat-fixation of cells prior to contact with the fixing fluid, sometimes resorted to by microbial cytologists, is a practice that induces shrinkage and hence is an agency yielding injury additional to the varying degrees of morphological and cytochemical destruction provoked by fluid fixatives.

Perhaps the most striking indication of the injurious influence of fixation with fluids is the total or partial collapse of the prominent central vacuole in yeast cells as seen under the light microscope. Even when such collapses are sometimes prevented, electronmicrographs reveal clearly the damage occuring in other parts of the cell, particularly to the fine structure of the nucleus and of the cytoplasm. Practically all of the disadvantages of fluid fixation can be overcome by proper freezing-drying and judicious postfixation treatments. The improvements potentially achievable with correct manipulations of these techniques are so appreciable as to make them especially desirable in circumventing, or at least

greatly reducing, problems of observation inherent to small cells. The instantaneous quenching of living yeast cells in liquid propane at a temperature of −175° C., followed by low-temperature drying *in vacuo*, suitable postfixation, and other steps ensure preservation of the large central vacuole in a manner not often matched by the usual methods of chemical fixation.

It is ironical that so extremely little use has been made of cytological freezing-drying techniques for study of microbial structure, in spite of the circumstance that allied techniques of lyophilization are widely used in other microbiological applications.

The most pronounced improvements that may be realized with freezing-drying are those affecting cytochemical applications in microbiology, both at the light and electron microscopical levels. As the structural and chemical changes induced in protoplasm by freezing-drying are minimal, it is clear that *in situ* localizations of enzymes and similar refractory substances may be achieved with appreciably reduced prospects of spurious reactions, inactivation, or diffusion of the component investigated. However, there is as yet no record in microbiology as far as I am aware, of specific cytochemical localization of enzymes following freezing-drying, although a beginning in this direction is being undertaken in my laboratory. On the other hand, the incertitudes and technical difficulties attending such localizations, both regarding specificity of reaction and unaltered spatial retention of substrate, are so formidable after the use of convential methods as recorded in the literature, that it seems extremely doubtful that claims of enzyme localization in bacteria, fungi, algae or protozoa are fully in consonance with the requirements of critical cytochemistry.

Interpretations at the ultrastructural level have, in general, posed the same questions in microorganisms as in work with the higher cell types. The great popularity of metallic compounds like osmium tetroxide and potassium permanganate derives from the ease with which they can be employed and the high electron scatter they provide. Indeed, their value in morphological studies has often been demonstrated, particularly in obtaining high image contrast. As, however, the stoichiometry of such compounds is poorly understood, it has not as yet been possible to exploit them for definitive compositional studies of microorganisms. While they reveal cellular membranes effectively, their nonselective affinities for protoplasmic constituents limits their value in such important problems as resolving the nature of bacterial and fungal nuclei, which show an unusual organization. Thus, in the remarkably interesting pictures of bacterial nuclei produced by several workers, it is difficult owing to the generalized staining yielded by metallic fixation (which also serves as an electron "stain") directly to correlate densely stained regions specifically to basophilia of the nucleus (or of the cytoplasm); this problem is compounded, furthermore, by the fact that slight alterations in procedures

result in widely varied morphological effects (Giesbrecht, 1958; Przybylski and Cortelyou, 1961).

An additional undesirable feature to be considered in interpreting microbial structure with the electron microscope is the extractive influence of fixing solutions, particularly potassium permanganate, described by Bradbury and Meek (1960). This effect is illustrated in yeast where the cytoplasm and nuclei possess characteristics of granulation and texture so remarkably identical that only the retention of nuclear membranes indicates the occurence of sectioned nuclei in the specimens (Conti and Naylor, 1959; Vitols *et al.*, 1961).

Perhaps the severest limitation of methods utilizing metallic fixatives is the inapplicability of cytochemistry in potentially important microbiological problems with the electron microscope. The electron scatter produced by the commonly employed inorganic metallic fixatives is of so high an order and so generalized, that it obscures the superimposed, far weaker images characteristic of the relatively lower molecular weight reaction products involved in many cytochemical or color reactions. If, however, a "clear" background of protoplasm is ensured, such as is obtained after freezing and drying, an opportunity is presented of utilizing certain reactions of high specificity. As an example may be mentioned the application of the periodate-Schiff method for ultrastructural cytochemistry of polysaccharides in yeasts. Provided that sufficient reactive groups are available and the quantity of organic dye bound by the substrate is of an order adequate enough to yield detectable electron scatter, as indeed is the case in this reaction, it is possible directly to visualize the morphological disposition and establish the identity of various polysaccharides, including molecules of glycogen, with the aid of enzymatic control tests. Such positive procedures contrast with the problems of ascertaining the identity of glycogen following the usual methods of fixation for electron microscopy, as in *Escherichia coli* (Cedergren and Holme, 1959) where the localization of glycogen, as clear "holes" in a dense background, is only inconclusively inferential.

Finally, an example of a procedure that produces very satisfactory electron scatter and image contrast and at the same time shows a high degree of affinity for nucleoproteins is the gallocyanin-chromalum method (Einarson, 1951). Used in yeast (Mundkur, 1960*a*; 1961) after freezing-drying and selective postfixation of proteins and polypeptides with organic vapor reagents such as 1,5–difluoro, –2,4 dinitrobenzene, it has been possible to achieve a marked selectivity of staining for basophilia and, thus, largely to circumvent the problems of morphological and chemical preservation attending the ultrastructural study of the yeast nucleus with the usual methods of fixation with inorganic salts.

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SECTION OF GEOLOGICAL SCIENCES

SOME GEOLOGIC FEATURES OF BEDROCK VALLEYS OF THE NEW ENGLAND COAST*

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Introduction

This paper presents some results of a study of the bedrock valleys of coastal New England. The study is a project under the research program of the United States Geological Survey, Ground Water Branch. Records of borings, chiefly for highway bridges, across 14 rivers or embayments (such as Narragansett Bay) were obtained from State Highway Departments and other agencies (FIGURE 1). Cross sections were prepared and studied. Original samples from some borings, especially in Connecticut, were examined. Collection of the data and nearly all the field examination were done by C. W. Spencer, who also prepared detailed cross sections. This paper is based on a more detailed account in preparation.

Each of the present streams of coastal New England is flowing on, or near, a bedrock valley: (1) which is wholly or partly filled with unconsolidated deposits, and (2) whose thalweg at or near the coast lies several tens to several hundred feet below present sea level. Most of the valleys are simply deep-lying parts of visible valleys, but a few are completely filled and concealed by deposits. Only the latter valleys can be truly called "buried." This paper deals with two aspects of the buried, or bedrock, valleys: the depths and origin of the bedrock thalwegs, and the origin of a younger set of valleys for which evidence lies in the stratigraphy of the fill contained in the bedrock valleys.

Principal Geologic Features of the Bedrock Valleys

Sections across the several valleys give information about three main points: depths of the thalwegs of the bedrock valleys, the stratigraphy of the fill, and depths of the thalwegs of younger valleys represented by an unconformity within the fill.

The section across the Thames River about 5 miles north of the shore (see upper part of FIGURE 2) is typical of the valleys of coastal Connecticut. Bedrock was cored in making the borings, giving good control on its surface. The altitude of the thalweg may be about -200 feet mean

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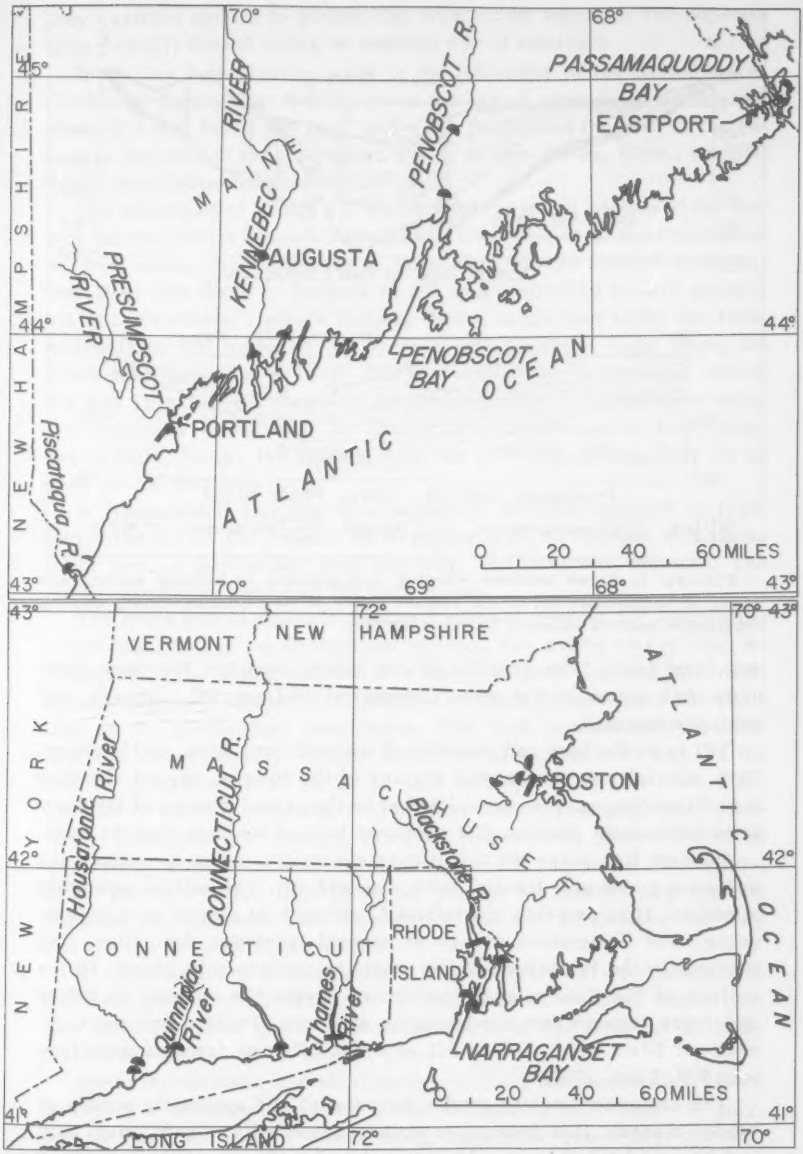

FIGURE 1. Sketch maps of parts of New England showing major rivers and locations of data sites. ▲ indicates site of borings or geophysical data. ▬ indicates section illustrated in this paper.

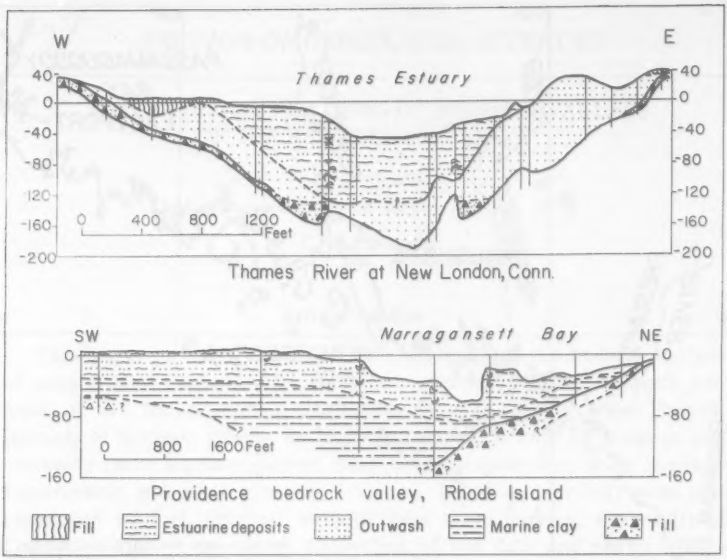

FIGURE 2. Cross sections showing configuration of bedrock surface and nature of sedimentary fill in the Thames valley at New London, Conn., and the Providence bedrock valley in Narragansett Bay.

sea level (msl). The deposits in the valley comprise the same three units that appear in the other Connecticut valleys: till, outwash, and estuarine deposits.

Till is at the base and consists of compact sand, clay, and boulders. This material was encountered at many of the borings, but not all; thus it is discontinuous. It is considered to be the ground moraine of the early or mid-Wisconsin glaciers that advanced beyond southern New England.

Outwash lies above the till. It consists mainly of fine to coarse sand and some gravel and, locally, some clay and silt. The unit is apparently stratified. It is probably glaciofluvial, although at places it is uniform enough and fine-grained enough to suggest lacustrine deposition. The outwash in the Housatonic valley contains considerable gravel. In the valleys of the Thames and Connecticut Rivers the outwash underlies and forms terraces that are traceable upstream. Those along the Connecticut River head at the limit of the Middletown ice readvance (see page 899, Flint, 1953).

The estuarine deposits overlie the outwash and apparently occupy an eroded channel. This material is usually described as "soft" clay silt, and fine sand. It is brown and has organic matter (peat and plant remains), and locally shell fragments. In the Thames estuary, the estuarine deposits extend upward nearly to sea level; and in some of the other valleys

they continue upward to present-day tidal marsh deposits. The deposits were probably formed during an eustatic rise of sea level.

A C^{14} age determination made in the laboratory of the United States Geological Survey (No. W-945), gives the age of some peaty material at 30 to 31.5 feet below sea level and a few feet above the base of the estuarine deposits in the Quinnipiac Valley at New Haven, Conn., as 5900 ± 200 years before the present (B.P.).

The lower part of FIGURE 2 shows a fairly typical section of the bedrock valleys that lie beneath Narragansett Bay. This is on the Providence bedrock valley, the middle one of three main valleys beneath Narragansett Bay. The depth to bedrock is not well controlled in this section, but it is in others. Bedrock thalweg depths range from about sea level just outside the border of the Narragansett structural basin along the Blackstone River, to at least -380 feet msl at the easternmost site in the Bay (FIGURE 1). Based on seismic reflection investigations using low frequency sound made by Woods Hole Oceanographic Institution, Woods Hole, Mass., the thalweg near the mouth of the Bay may be as deep as -350 feet msl.

In Narragansett Bay the unconsolidated deposits comprise at least four units: till on the bedrock, an overlying clay, an outwash unit whose lower part is interbedded with the clay, and estuarine deposits. The section illustrated shows all but the outwash.

The lower unit is compact, unsorted material, typical till, correlative of the basal unit in the Connecticut valleys. The middle unit of clay, as described in the boring records, is a gray, compact clay and silt which at many places is laminated. Although it contains silt and some fine sand, clay is the predominant constituent. This unit is penetrated in other sections and apparently occurs extensively in Narragansett Bay. In the section illustrated (FIGURE 2) the unit is at least 100 feet thick. Clay exposed in old clay pits, observed by past workers (see page 162, Woodworth, 1896; page 210, Hyyppä, 1955; and pages 26-27, Bierschenk, 1954) may belong to the same unit. Antevs (see locality 142, pages 189, Antevs, 1928) reported varves from the upper part of the deposits, but Hyyppä believes that the clays were deposited in the sea. We believe the clay and silt are probably mostly marine.

In other sections in Narragansett Bay the clay is interbedded with the lower part of an outwash unit. In grain size the outwash ranges from fine sand to coarse gravel in different parts of the area, but is fairly uniform and well sorted at any one place.

Above the outwash, and also locally overlying the marine clay, is the last unit – estuarine deposits. These consist of soft, brown to gray, organic clay and silt with some shell fragments. These beds are considered to be estuarine deposits, as are the similar ones in the valleys of Connecticut. They rest on an irregular surface, apparently a channel eroded in the underlying deposits.

The upper part of FIGURE 3 is a cross section of the Charles buried valley in Boston, Mass. The borings penetrated bedrock that was cored; hence configuration of the bedrock surface is fairly well controlled. The thalweg is about at -240 feet msl. The thalweg depths in several other sections in the Boston Basin lie at about this elevation, and suggest an erosional level at about -250 feet msl.

The deposits in the valleys comprise five units, not all differentiated in the section shown (FIGURE 3). The units are: (1) till, the Boston till of Judson (1949) at the base; (2) a thick body of marine clay and silt (Boston clay of Judson, 1949) that locally is overlain by and around the margins of the basin is interbedded with (3) outwash; (4) a body of sand and gravel that may also be outwash; and (5) a unit of estuarine deposits composed mainly of silt and clay with interbedded peat and other organic materials. In FIGURE 3 the till and the overlying clay are differentiated, but the remaining units are combined.

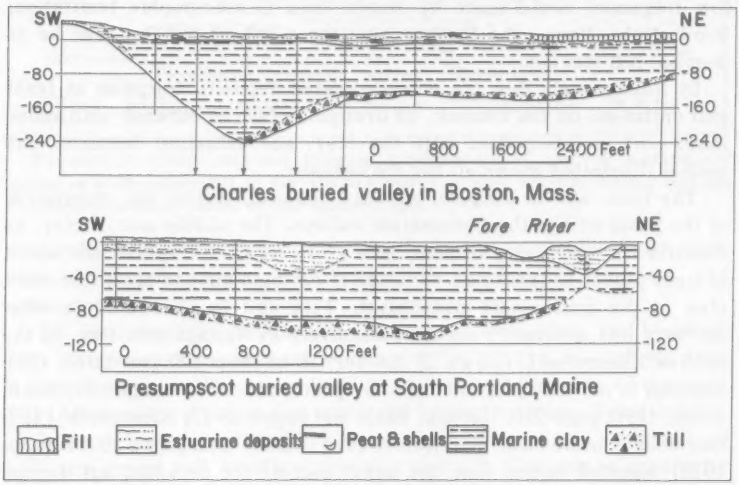

FIGURE 3. Sections of buried valleys in Boston, Mass. and at South Portland, Me.

The basal till is presumably equivalent to the basal unit in Narragansett Bay and the coastal valleys of Connecticut. The Boston clay is variously described in the boring records as loose to compact gray clay. This unit was deposited either at the margin of glacier ice, or when ice was not far away (see page 22, Judson, 1949). The overlying material (units 3 and 4), thought by Judson to be separated from the clay by an erosional unconformity, may be outwash from a readvance and retreat of the nearby ice. In turn, the uppermost unit contains fresh- and salt-water peat, marine silt, and finally salt-water peat all attesting to a rise in sea

level to the present time. This last unit belongs to the estuarine deposits of this paper. Judson postulated two periods of lowered sea level and subaerial erosion in this sequence: one after the deposition of the Boston clay of Judson (1949), and the other just before deposition of the estuarine deposits. In the earlier one, streams are thought to have been graded to a sea level about 90 feet below the present level. The estuarine deposits along the Charles River rest on an erosional channel that reaches at least 40 feet below present sea level in Boston, and presumably is deeper beneath Boston Harbor. It may also have been graded to a position about 90 feet below present sea level.

The lower part of FIGURE 3 is a section across the Presumpscot buried valley near Portland, Me. The borings went to "refusal;" thus the bedrock surface is approximate. The lowest point seems to be at about -120 feet msl.

The bedrock is overlain by till at most of the borings. The till in turn is overlain by a body of clay as much as 100 feet thick. This unit is described in the boring records as gray or blue-gray clay, silty clay, or clay and silt. It is soft, but apparently not so loose as overlying estuarine deposits. The material extends above sea level, is exposed at a number of localities in the area, and has been mapped along the Maine coast by a number of geologists. The latest work in the vicinity of Portland has been done by Bloom (1959) who called these beds the Presumpscot formation. He believes that the clays are a marine deposit of glacial rock flour with a few ice-rafted boulders and cobbles. The implication is that glacial ice was at the most a few dozen miles away. One of us (J.E.U.) has mapped similar deposits in the Passamaquoddy Bay area, where apparently they, too, were deposited when ice was not far away, and has seen similar beds in the vicinity of Portsmouth, N.H.

The deposits of marine clay and silt that occur all the way from eastern Maine to Boston Harbor, and perhaps also in Narragansett Bay, were doubtless deposited under the same general conditions – as glacial marginal clays in the sea that invaded the land immediately or closely following withdrawal of ice. However, it is not certain that they are all of the same age.

In the Presumpscot bedrock valley the marine clay is in turn overlain by estuarine deposits, which rest on an erosion surface. The lowest part of this erosion surface lies at about -40 feet msl in this section.

The bedrock configuration and stratigraphy of till in the submerged valleys near Passamaquoddy Bay have been described briefly previously in this publication (Upson, 1954). The marine passages overlie a bedrock valley system whose thalwegs, on the basis of subbottom investigations made by sonar, reach depths of about 400 feet below sea level, and appear to be graded to a base level somewhat below this depth.

The glacial deposits in this area are complex, but where they occur within the bedrock valleys, and where they have been explored by borings,

they have two chief units: a thin, locally washed till at the base, overlain by a thick unit of laminated or banded marine clay and silt. This marine unit apparently has not been channeled below sea level, as were the similar deposits farther south, and there is no overlying unit of estuarine deposits.

Summary of Data on Depths of Bedrock Thalwegs

The approximate elevations, below mean sea level, of the low points on the thalwegs of the bedrock valleys as determined or estimated from the sections studied are shown on FIGURE 4. The rivers can be identified by referring to FIGURE 1. At first glance there seems to be no system to the depths. However, two levels of erosion below present sea level may be recognized: one at about -200 to -250 feet and one at about -400 feet or a little lower.

The projected slope between the two points on the Housatonic bedrock valley reaches about -200 feet in the middle of Long Island Sound. The thalweg of the Thames is at about -200 feet. A reach of several miles on the Blackstone bedrock valley in the western part of the Narragansett Bay area is at about -200, and the valleys at Boston may be graded to a -250-foot elevation.

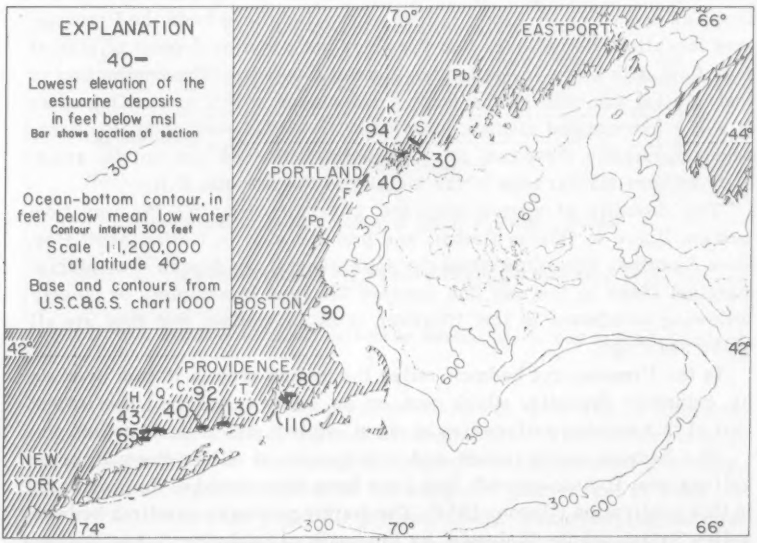

FIGURE 4. Map of the New England coast showing elevations of the thalwegs of bedrock valleys. Letter symbols designate rivers, as follows: H, Housatonic; Q, Quinnipiac; C, Connecticut; T, Thames; Pa, Piscataqua; F, Fore River (Presumpscot buried valley; K, Kennebec; S, Sheepscot; Pb, Penobscot; SC, St. Croix (Passamaquoddy Bay).

The Connecticut River thalweg might fit this elevation, but may be deeper. The -200-foot figure shown on the map is a minimum estimate. The figure for the Quinnipiac, deeper than -280 feet, looks out of line. However, this section is on the relatively less resistant sedimentary rocks of the Triassic Neward Group, and either may show overdeepening by glacial scour, or represent an upstream extension of a lower erosional level.

For the lower level, one accurate depth, at about -380 feet msl is on the crossing of the Taunton-Sakonnet bedrock valley in Narragansett Bay (the northern of the two numbers shown). The other number at Narragansett Bay is an approximation from seismic reflection profiling using low-frequency sound. In the far north, at Passamaquoddy Bay, two sets of data from sonar subbottom soundings for places several miles apart also give thalweg depths a little deeper than 400 feet below sea level. Projecting the slope between the two figures on the Penobscot River (-45 and -120) also gives a depth greater than 400 feet at the outer margin of Penobscot Bay.

The figures for the other Maine valleys range from -90 to -160 feet msl. The significance of these shallow depths is not known at this time.

Summary of Data on Unconsolidated Deposits and the Thalwegs of Pre-estuarine Valleys

The unconsolidated deposits within the bedrock valleys of coastal New England consist mainly of glacial deposits – mostly outwash along the Connecticut coast, and mostly ice-marginal marine clay and silt at least from Boston Harbor, and possibly from Narragansett Bay, north. At the base is thin till, which is doubtless early to mid-Wisconsin in age. In all the valleys except those of eastern Maine, the glacial deposits are overlain unconformably by estuarine deposits. These are considered to be approximately contemporaneous everywhere, and to represent a late general rise of sea level relative to the coast. In the areas where the marine clays occur, the sea was initially high against the land, then declined relatively, and later rose to its present level. On the other hand, in extreme eastern Maine, evidence for the relative decline and then rise of sea level is lacking, and the sea apparently simply moved relatively downward from its late-glacial high level to the present level (see pages 292-293, Upson, 1954). However, the relative position of land and sea at the time could have been such that a decline and rise of sea level took place, but left no trace in the form of erosional channels.

The unconformity at the base of the estuarine deposits is the second main feature of concern in this paper. The approximate elevations of the low points on this surface are plotted on FIGURE 5. The figures along the shore of Connecticut and Rhode Island make a pattern that might reasonably fit a stream drainage system passing eastward through Long

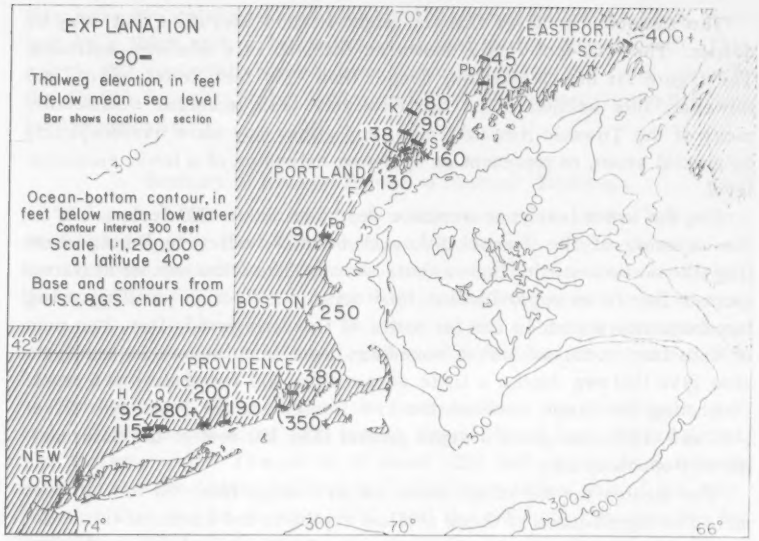

FIGURE 5. Map of the New England Coast showing elevations of the thalwegs of pre-estuarine valleys. Letter symbols designate rivers, as follows: H, Housatonic; Q, Quinnipiac; C, Connecticut; T, Thames; Pa, Piscataqua; F, Fore River (Presumpscot buried valley); K, Kennebec; S, Sheepscot; Pb, Penobscot.

Island Sound, and then southeastward off the end of Long Island. This system would be graded to a level on the order of -150 feet msl.

The elevations at Boston Harbor and along the Maine coast are shallower, and, discounting the -94-foot figure, suggest progressive shoaling northward and eastward, culminating in apparent absence of the unconformity in Passamaquoddy Bay near Eastport.

Conclusions

The early or mid-Wisconsin till occurs on the bedrock surface of all the valleys. Therefore, the bedrock valleys are believed to have been developed largely before the Wisconsin; and the present depth of the thalwegs below sea level is no measure of Wisconsin lowering of sea level. The deep levels, on the order of -400 feet, may represent eustatic lowering of sea level in early Pleistocene time. On the other hand, they may represent the last episodes of Tertiary stream erosion, and, if so, probably indicate subsequent crustal downwarp. The depths are believed not to be due in appreciable measure to glacial scour.

There are several possible explanations for the unconformity at the base of the estuarine deposits within the fill. Evidence at present seems to favor a period of lowered sea level, on the order of -150 feet below the

present level, with resulting subaerial erosion. The northward shoaling of the thalweg depths of this surface, and its absence in extreme eastern Maine, may be due to incomplete crustal recoil remaining at the time of sea-level decline. The sea-level decline would coincide with a late glacial, probably Valders or Mankato, ice readvance. Deposition of the estuarine deposits accompanied the last general eustatic rise in sea level. Age of peaty material at -30 to -31.5 feet in the estuarine deposits of the drowned valley of the Quinnipiac River, about 5900 ± 200 years B.P., is in accord with this inference.

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TESTING AND THE SELECTION OF SCIENTIFIC PERSONNEL*

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For a problem as complex as the selection of scientists one does not expect a single procedure or method or new drug to provide the answer. Barring a miraculous discovery that would make available the single indicator of future scientific success, the most fruitful approach lies in analyzing the problem and determining which procedures may contribute to its solution. It is in this context that I propose to consider the role of tests in selecting scientific personnel.

In many respects the general procedure for selecting scientists is the same as that for selecting typists, lathe operators, clerks, or any other workers. There is a need for the services of a certain type of employee; available applicants are considered in the light of the felt need; and a decision is made to hire some of them. To determine whether the procedure is operating properly, employees are rated after a period of time and a study is made of the relationships between the factors that entered into the decision to hire and the ratings of performance. If possible, changes are made in the hiring process to assure the selection of people more likely to receive the better ratings.

A decision to hire may be based on the results of an interview, the evaluation of educational background and previous work experience, the outcome of a physical examination, the results of test scores and, perhaps, various other factors that are seen as relevant to the specific situation. The prospective employer rates the applicant on these factors, sometimes without conscious knowledge of how much weight he is attaching to each, and reaches a decision. In effect, the factors are acting as predictors of job success.

It is important to remember that tests are only one of the types of predictors for selection. The function of tests is to provide *additional* information that will aid in the formulation of a proper decision. It is *not* the function of tests to replace all other kinds of information that could be gathered and evaluated.

The evaluation of the predictors used in a selection procedure necessarily depends on the availability of criteria of satisfactory performance. More than anything else, the problem of securing suitable criterion measures of scientific performance reveals the complexity of the task of selecting scientific personnel. How should a scientist be evaluated?

*This paper was presented at a meeting of the Division on April 17, 1961.

Most people will agree that creativity and productivity are highly desirable quantities in scientists. It is extremely difficult, however, to obtain valid ratings of creativity. Is the scientist who produces many imaginative approaches that ultimately are impractical to be rated more or less creative than the man with an occasional idea that turns out to be valuable? How long should a scientist work on a problem before he can be properly evaluated? For scientists working in teams, how are distinctions made among the members in regard to the value of their contributions?

The concept of creativity is rather amorphous and means different things to different people. Some investigators have attempted to describe the characteristics of creative individuals. Among such characteristics have been noted: a driving absorption in one's work, a preference for complexity in phenomena, a disposition toward integration of phenomena, a high degree of intellect, and synthesizing ability and flexibility. In the introduction to their book "*Creativity and the Individual*" Morris Stein and Shirley Heinze[1] have written: "The most striking features of the literature on creativity are the variety of approaches that investigators have followed, the variety of results that have been obtained, and the numerous factors about which suggestions and speculations have been made.... There are those who have designed experiments, or used psychological tests, or conducted interviews, or some combination of these approaches, while others speculated about creativity on the basis of biographies they read or experiences they had.... One person or another has argued for the importance of pregenital drives, defense mechanisms, defenses against defenses, insanity, sanity, the desire for immortality, the need for order, the significance of sublimation, and the importance of self-actualization."

Although the vast amount of literature on aspects of creativity may be confusing and sometimes disheartening, it represents a necessary attempt to obtain useful information. Without having adequate understanding of what characteristics are associated with creative performance, it is impossible to evaluate individuals with respect to these characteristics. Having identified the characteristics, not only can we improve the ratings but we can proceed to develop measures that will predict these ratings.

Creativity is a dramatic concept that is obviously relevant to the work of scientists. It must be kept in mind, however, that it is not necessary for all scientists to be highly creative individuals. In a recent issue of the *Occupational Outlook Quarterly*,[2] it was estimated that 800,000 scientists and engineers were employed in private industry as of January 1959. It is frightening to think of the possible consequences of having all of these individuals highly creative in their work. It may be more realistic to hope that a relatively small percentage will be highly creative and most if the others highly productive. The plodding scientist who uses his special knowledge to try out the ideas of another scientist

or who works to maintain standards is a very valuable member of the scientific community. The implication for evaluation is that multiple criteria must be considered and that different predictors may be effective for different criteria.

Despite criticisms that can be leveled at many of the criteria now in use, there have been numerous attempts to evaluate tests in the light of these criteria. In some instances, a special effort has been made to improve the criteria before judging the tests. The studies provide clues to what may be expected of tests and often point up weaknesses in the criteria themselves.

A variety of types of tests has been used for predicting the performance of scientists. A partial list would include the following:

(1) *Tests of general mental ability, suitable for the intellectual and educational level of scientific personnel.* These include such tests as the Miller Analogies Test, the industrial form of which is called the Advanced Personnel Test, the Terman Concept Mastery Test, and measures of mathematical reasoning ability. Although it may be maintained that high intelligence does not necessarily lead to creativity, we should expect creative scientists to come from the high-intelligence group.

(2) *Tests of proficiency in more specialized areas.* For example, the Minnesota Engineering Analogies Test has been found by many companies to be very helpful in the selection of engineers. Tests of mechanical comprehension, spatial visualization, and abstract reasoning have also been found to be useful predictors of scientific success.

(3) *Interest measures.* In several organizations, selected scales of the Strong Vocational Interest Blank and the Study of Values by Allport, Vernon, and Lindzey have offered leads for further study.

(4) *Tests of productive or creative thinking.* In these the subject may be presented with situations, often hypothetical, and asked to propose possible consequences. Some tests of this type have been strikingly effective in specific instances, showing high correlations with measures of creative ability and originality. A limitation of this type of instrument is the difficulty of evaluating the responses and the need for regular review of the items to determine their continued suitability. The advances of science may convert many of the imaginary situations of this year into reality next year.

(5) *Measures of word association, visual imagery, associational fluency, and ideational fluency.* Such tests have been found promising in some studies. Many of these are still in research stages and undergoing experimental verification.

(6) *Special apparatus such as the Logical Analysis Device.* This is a simple machine that can be used to observe how an individual goes about solving a problem when he has been taught the proper procedure and given access to all the information he needs. The style of attack has been

found to vary over quite a range. This device has been found useful in predicting the effectiveness of computer programmers and in distinguishing between "doers" and "thinkers" in a group of engineers.

(7) *Personality measures such as the Rorschach and Thematic Apperception Test.* Anne Roe[3] has used these tests along with other procedures in intensive studies of eminent scientists. Clues pointing to differences among various scientific groups have emerged from some of the studies. I do not believe, however, that Roe would recommend these personality measures as selection devices.

This is not an exhaustive review of tests that have been used to predict scientific success but it may serve to indicate that a number of types and a much larger number of specific tests have been studied. It is desirable to keep in mind that although many of these tests have been found useful in some situations, they have also been found useless in others.

The problem of using tests is complicated by being intimately related to the problem of evaluation of personnel and no single test or group of tests is universally effective. Furthermore, tests should never be studied alone in the selection situation, but in conjunction with other predictors that may be obtained for applicants, such as interview evaluation, eductational background, *etc.* Obviously it would be most desirable for each organization interested in using tests to have a highly trained person design a study. This design would take into consideration the particular conditions existing in the organization, and indicate the tests to be tried. An important part of the plan would be a careful description of how the tests are to be evaluated. Thinking through the problems of the criteria for evaluation may be highly profitable even if particular tests prove ineffective.

As is often true in the work of the scientists who have been selected, frustration is a concomitant of work in the personnel selection area. The adoption of a procedure that is scientific in its approach in evaluating all available information, including test scores, will reduce frustration much more than reliance on the claimed merits of a specific test.

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RESULTS AND ACHIEVEMENTS TO DATE: THE FAILURES AND SUCCESSES OF CURRENT GUIDANCE PRACTICES*

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In the winter edition of the *Journal of Counseling Psychology*, 1958, C. Gilbert Wrenn[1] published an interesting lament. He commented on the status of counseling psychology and concluded: (1) that counseling psychology has the lowest rating of any specialization in psychology requiring the Ph.D; (2) that no one has yet developed a satisfactory theory of vocational choice; and (3) that B. F. Skinner's research in learning suggests that counseling psychologists may be reinforcing the "sick" behavior of their clients. "How much more excitement," exclaimed Wrenn in despair, "can a no-longer-young psychologist handle."

The Struggle for Purpose in Guidance

Most readers of this periodical know that Wrenn is now working on a project organized by the American Personnel and Guidance Association, Washington, D.C., to define, if possible, the terms "personnel" and "guidance" and to decide what personnel and guidance workers and/or counseling psychologists should be doing.

The guidance movement lacks clarity of purpose for good reason. When Western man uses his science to investigate himself and the society he has produced, he is confronted at once with a paradox. For his science implies that behavior is caused and predictable, but he has built his society upon the idea of personal responsibility and freedom. The behavioral scientist finds himself, therefore, attempting to explain, predict, and control human behavior in a society where men believe that they are free and responsible for their own acts. All behavioral scientists face this paradox. Since the guidance worker, in part at least, attempts to be a behavioral scientist, he must face this paradox also.

Edward Joseph Shohen, Jr.[2] has made this point clear: "The technical power of science and its growth in prestige has led scientists to divorce themselves from the humanistic traditions represented in history, literature, and philosophy. This conflict is only symbolized by, not restricted to, the tension between behavioral scientists and professors in the humanities on university campuses. While it is true that the humanistic traditions embody conservative as well as liberal conceptions and, like any tradition, tend to crystallize at times into bigotry and closed-mindedism, they also are the carriers of recurrent insights and ideas about the most rewarding relationships between man and man, man and society, and – for those who are interested – man and those Powers other than

*This paper was presented at a meeting of the Division on March 20, 1961.

himself that he perceives in the universe. Such ideas, confused and contradictory as they sometimes are, constitute the basis of wisdom, guides evolved over history to the choices men must make in living their lives. They represent the behavioral prescriptions in varied and often incompatible terms that define the varieties of the "good life" that the social sciences can be instrumental in achieving but which science itself cannot define."

Guidance workers have been slow to recognize this contradiction in assumptions. We have not always understood that science is a technique that may be used to achieve a variety of purposes. The fact that values lie outside the techniques of science and that science is not an end in itself has not always been clear to us. The field of guidance has not, as yet, produced men of sufficient stature to deal with this fundamental contradiction. The Western World, in fact, has not produced such men. However, guidance workers should at least appreciate the magnitude of the problem they face. They should understand the inconsistency of believing that behavior is caused while also believing that men are free. We should certainly stop the unproductive business of trying to escape this paradox through opinion polls, discussion, and surveys.

Guidance workers face a second paradox concerning the way education should be conducted in our democracy. Thomas Jefferson sponsored the principle of student selection for education. Andrew Jackson rejected it. American educators concurrently accept and reject the principle of student selection.

You will recall that Jefferson's plan for educating the people of Virginia was based upon the principle of selection. He proposed to form in every county small districts of five or six miles square and in each of these to establish an elementary school. The boy of "best genius" in each elementary school was to be selected each year and sent forward to grammar school and the best half of the boys in the grammar schools were eventually to be sent on to the College of Virginia.

Jackson rejected the principle of selection. The Jacksonian doctrine of education is well expressed by a historian of the Jacksonian period, George Bancroft:[3] "Let the waters of intelligence, like the rains of heaven, descend upon the whole earth... The prejudices of ignorance are more easily removed than the prejudices of interest; the first are blindly adopted; the second are wilfully preferred! Intelligence must be diffused among the whole people; truth must be scattered among those who have no interest to suppress its growth... It is alone by infusing great principles into the common mind that revolutions in society are brought about. They never have been, they never can be, effected by superior individual intelligence."

Today education for all is accepted as a necessity. The tax-supported public school is taken for granted. All responsible citizens subscribe to the principle that each individual in our society is entitled to the most

appropriate and best education for him as a person. The opportunity to develop one's capacities to the full has risen to the status of life, liberty, and the pursuit of happiness as an inalienable right.

However, we cannot agree as to what constitutes the best education for each individual. Should education be "basic" or "progressive?" What about the question of separate but equal educational facilities? Should financial need be taken into account in awarding scholarships? Is an opportunity to try one's hand at tests of admission to an educational program enough? Or should everyone have an opportunity to try his hand at the program itself? If an individual fails a program, should he be permitted to try again? If so, how many times should he be permitted to fail and try again? These questions are "old hat" to guidance workers, but unfortunately, guidance workers have contributed little to the task of providing satisfactory answers.

Guidance workers face a third paradox within the field of guidance itself. Most workers think of themselves as specialists: specialists in counseling, specialists in testing, specialists in the development and use of career information. They think of the guidance movement as an effort to overcome the tendency of systems of mass education to produce specialists and thereby become impersonal. Guidance workers find themselves in the awkward position, therefore, of being specialists in overcoming the harmful effects of specialization!

Dael Wolfle[4] has estimated recently that knowledge in the natural sciences is doubling every 15 years and that knowledge in the social sciences is doubling every 30 to 45 years. The magnitude of information available and the complex nature of modern society force man to specialize. However, specialization brings a host of problems, particularly in education. There are extremely difficult problems arising from the fact that teachers and students must specialize in subject matter areas. The problems involved in dividing the task of educating an individual are overwhelming.

The confusion, uncertainty, and vagueness of purpose characterizing the field of guidance today must be understood and evaluated, it seems to me, in terms of the paradoxes I have described. Most unsolved problems in guidance are related to unreconciled assumptions. As the world develops a clearer conception of the function of science, as the nation makes up its mind about the selection of students for education, and as guidance workers decide whether they are specialists essentially or coordinators of service essentially, guidance objectives must evolve.

Viewed from this perspective, the struggle for purpose in guidance has new meaning. It is obvious that we cannot hope to find purpose through a simple devotion to science alone. We are not likely to discover purpose through the behavioral sciences from which we have borrowed many of our techniques. We cannot discover purpose within the confines of our own professional organizations. Our purpose becomes that of

participating in the continuous struggle of Western man for purpose: purpose nationally and purpose in the world itself.

From this lofty view, what can be said of our successes and failures in guidance during the 50 years the movement has been in existence? What have we done? What have we failed to do? What about the future of this work to which so many of us have given our energies, our best efforts, and our professional lives?

Research in Guidance

In 1933 Strang[5] examined the research that had been done in guidance and concluded that much had been attempted but little accomplished. In 1957 Ruth Barry and Beverly Wolf[6] brought the Strang examination of guidance research up to date and reported that Strang's conclusion still applied. They deplored the paucity of guidance research. They complained that the question "What is guidance research?" has never been answered. They documented the fact that research and evaluative techniques are neglected in guidance training, and they concluded that improvement will probably not take place until guidance workers are better prepared to do research.

The fact is that today's guidance practices have not been evaluated scientifically. We simply do not know how successful guidance practices such as orientation, faculty advising, psychological counseling, placement, and student self-government have been. I can describe guidance systems that are believed to be successful. I can review the meager attempts that have been made to evaluate guidance practices. However, I cannot produce conclusive scientific evidence that guidance workers have succeeded or failed. The best I can do is to submit my considered judgment as to our present status.

Successes

I shall describe what I regard as our successes in guidance in terms of three general statements.

(1) *In the secondary schools and colleges of the United States guidance has achieved recognition as a necessity.* It is well known that guidance is considered an important aspect of national defense. It is ranked with mathematics, science, and languages as a vital area to be strengthened through the provisions of the National Defense Education Act. During the fiscal year, July 1, 1959 to June 30, 1960, 20 million dollars were dispensed by the federal government in support of guidance programs. There are approximately 11,500 counselors in the secondary schools of the United States. One counselor is now available for every 600 students. Twenty years ago the ratio was 1 counselor for every 3000 students. During the years 1959 and 1960 seven million tests were given for guidance purposes. Fifty states, the District of Columbia, and three terri-

tories participate in federally sponsored programs. State departments of education employ approximately 180 full-time workers to supervise guidance activities.

Guidance services are recognized and well established in the colleges and universities of the United States. E. G. Williamson[7] has shown that other-than-classroom services have always been available to students in institutions of higher learning. Where students are, things go wrong, and something has to be done. The present organizational pattern of student personnel services, which includes guidance, was well established by 1930. In the beginning, guidance programs in institutions of higher learning were corrective; later they were preventive; today we hope they contribute to the development of each student as a person.

(2) *Guidance workers have avoided the search for an easy answer and have faced the fact that the helping situation has many dimensions.* Guidance has not been destroyed or replaced by any of the numerous educational and other social innovations that came to flower during the first half of the 20th century. It survived competition and became a necessity. Guidance workers were too close to the troubles of the day to be led astray by easy solutions or to be deceived for long by the impractical. Guidance soon broke the confines of the vocational guidance movement that gave it birth. Progressive education made an unsuccessful attempt to ingest guidance. Guidance workers refused to become merely psychometrists, for tests left too many questions unanswered. They have been reluctant to regard themselves as mental hygienists, for they cannot accept the idea that persons with behavior problems should always be treated as if they were victims of some disease state. They have joined no school of counseling, for they use the interview essentially to influence the growth and development of individuals and not to practice psychotherapy. Most guidance workers have found the group dynamics (or group processes) movement less than satisfying, and few have made the pilgrimage to Bethel, Me.

The guidance worker both coordinates and administers services. While he brings to the helping situation skill in testing, skill in interviewing, and a knowledge of educational and work opportunities, he recognizes (1) that growing and developing individuals need help from a variety of sources, and (2) that some need help from individuals and groups representing not only different fields of interest and specialization but different levels of competence. He knows that peers, parents, and teachers may help. He knows that groups, agencies, and institutions may help. He knows that an interview may be conducted for many purposes and at different levels of intensity. He knows that an interviewer may establish many kinds of relationships with an interviewee. He recognizes permissive, nonevaluative counseling as but one of these relationships. The guidance worker does not cringe, therefore, when he becomes involved in certain necessary and important administrative procedures.

The guidance worker also knows that assistance from adults can harm as well as help adolescents. He knows that character is formed and maturity is achieved when students are required to handle many of their own problems. He knows that psychological explanations can be used by students to avoid responsibility. He knows that the problems and frustrations of normal living can be the stuff out of which strong men are made.

The guidance worker understands that the task of assisting the college student without weakening the student's initiative and self-reliance, is difficult, complex, and often fraught with failure. He struggles constantly, therefore, to discover the kind of help students really need and to perfect the art of administering that help constructively. He does not subscribe to the myth that a simple "scientific" solution can be discovered for all human relations problems.

(3) *Guidance workers have maintained their independence from clinical psychology, education, social work, and psychiatry.* While guidance workers cannot agree among themselves, they unite to resist adoption or capture by any other group. The American Personnel and Guidance Association is composed of six obstreperous divisions with a combined total membership of 13,000 persons. The National Association of Women Deans and Counselors and the National Association of Student Personnel Administrators have refused to become divisions of the American Personnel and Guidance Association. The National Association of Women Deans and Counselors is a unit of the National Education Association, Washington, D. C. However, the American Personnel and Guidance Association has refused to affiliate with the National Education Association. The American Personnel and Guidance Association has no official connection with the American Psychological Association. It has little interest in the American Psychiatric Association. Both of these organizations also have headquarters in Washington, D. C.

Since personnel and guidance workers have remained sceptical of the mental health idea, they have not permitted the center of gravity of their job concept to shift from "development" to "therapy." Most workers have resisted the pat answers of psychiatry to the problems of individual behavior. They have found it impossible to de-emphasize the concept of individual responsibility. They have not adopted the language of the psychiatric clinic as have clinical psychologists, social workers, and – to an extent that is amazing – even elementary school teachers. Such terms as parental rejection, sibling rivalry, ego strength, escape mechanism, personality dynamics, transference, and psychosexual development, do not roll off the tongues of guidance people quite so easily as they roll off the tongues of other workers. Guidance workers have been reasonably successful in the struggle to retain their unique function without being drawn into therapeutic relationships for which they are not prepared.

In summary, then, our successes are as follows: (1) guidance has

achieved recognition as a necessary educational service; (2) guidance workers have established a multidimensional concept of the helping situation; and (3) guidance workers have demonstrated their unique function in education, and they have maintained their independence from other professional groups.

Failures

As the achievements of guidance workers are related to the struggle for purpose, so are their failures.

(1) Guidance workers have failed to contribute significantly to a reconciliation of the paradox of predictable behavior and individual responsibility.

(2) They have failed to contribute as they should have contributed to a solution of the problem of student selection. Guidance workers know more about the process of selecting students for educational programs than they have been willing or able to put into practice. They have failed to provide the leadership necessary to establish effective selection procedures.

(3) Guidance workers have failed to produce a body of knowledge, a repertory of techniques, and a philosophy that entitles them to recognition as a full-fledged profession: (a) we have no clear guidance vocabulary; (b) we cannot agree as to the content and methodology of an adequate training program for guidance workers; (c) we cannot decide whether the guidance worker should provide client services primarily or coordinate the services of others primarily; (d) we cannot agree as to the kinds of other-than-teaching services that are appropriate in an educational institution; and (e) we have not established a united professional association.

The Future

Despite our failures, I am optimistic about the future of guidance. I am naive enough to believe that a time of crisis is a time of special opportunity. I also believe that conflicting ideas have creative potential. I am convinced that the need for guidance is real and universal, and I have faith in the ability of guidance workers to find, within the context of world struggle for purpose, clear and compelling objectives for the guidance movement.

College counselors, I am confident, will eventually take considerable responsibility for facilitating changes in the behavior of students. They will marshall the guidance resources of the college and community for the use of students and faculty members. They will help students discover and adopt appropriate goals. They will find ways to motivate students toward higher achievement and, when a student is unable to cope with his situation, they will find ways to help him without weakening or destroying his initiative and self-reliance.

College counselors in time, I believe, will learn to live with and contribute to both science and a free society. They will use the techniques of science to explore the complexities of the helping situation and to discover the positive and negative elements in it. However, they will also use the techniques of science to promote the values upon which true democracy rests: the right of the individual to develop his capacities to the full; the right of the individual to be responsible; the right of the individual to be more than a mechanism, the right, in fact, to be a human being.

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DIVISION OF MATHEMATICS

SYMBOLIC LOGIC AND COMPUTING MACHINES: SOME GENERAL REFLECTIONS AND PREJUDICES*

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The title of this paper is perhaps misleading. We are part of a small research group which has studied for a number of years the interrelationship of logic and computing machines. Although logic in many cases has served as a special aid, not all of the projects we have undertaken (for example, machine learning) have borne strict relationship to that subject. Nevertheless we believe these various projects to be meaningfully related to one another; therefore a broad statement of our diverse experience and prejudice might reasonably be called "Symbolic Logic and Computing Machines."

If we raise the question generally wherein logic might concern the computer and vice versa, it is helpful to think of the computer in its threefold guise. First (and hindmost), a computer is a body of hardware. Various "black boxes" are tied together to form larger black boxes, which in turn connect up with still more black boxes. These boxes, by and large, are input-output devices that may or may not retain information in transit for significant periods of time. The smaller, more elementary ones often perform operations that admit of surprising correlation with elementary particles from logic, specifically those of truth-function theory.[1] The letter is that branch of the subject that deals with connectives such as *and, or, not,* and then more complicated connectives that can be derived from these. Because of this correlation, we can sometimes reduce an engineering question to a logical one. Two typical problems upon which logical studies might (hopefully) shed light are: (1) which *selections* of boxes, viewed logically, will best serve the needs of design, and (2) how are the boxes *to be put together* most effectively in given cases ?

In its second guise, the computer, without reference to hardware, is a set of abstract operations, generally upon binary numbers. Here again there are possible correlations with logic. We combine computer operations in various ways to produce computer programs. The latter may be viewed as effective functions that generate given outputs from given inputs. Such abstract questions as which functions are effective or which domains of problems can be solved by a simple method stated in advance fall within the province of logic.

*This paper was presented at a meeting of the Division on March 8, 1961.

In its third, most important role, the computer is a source of problem-solving power. Here there is great concern not only to define the limits of that power but also to bring it to bear effectively on great varieties of problems. The logician might typically pose the question how well the machine can do logic, in the sense of testing nontrivial formulae for theoremhood.[2] He might then attempt to set up powerful theorem-testing programs.

In a brief paper it would be pointless to try to summarize our different projects and results, much less the general state of the art. On the other hand, we have been asked to speak with generality and not to confine ourselves to a given issue. The compromise we adopt is as follows. There are certain root points of view we have come to accept, largely as a result of hindsight. These, once formulated, we have found helpful, even though in some cases they are rather trivial and in others are not accepted by the majority of our colleagues. We do not claim originality for any of them. Nevertheless we feel they add up to a certain "know how," and therefore we shall present a limited statement of them.

The first observation we propose to make is that *a single-ballot election proves little.* A surprising number of so-called "computer experiments" are nothing more than single-ballot elections. Suppose we visualize a system S for solving problems P. We believe that a certain factor F, if incorporated into S, will prove helpful. An "experiment" is then run as follows. A somewhat simplified system S, incorporating F, is embodied within the computer. Some elementary problems P are posed, and some solved. The experimenter then announces positive confirmation of the thesis that F helps S solve P. The difficulty with the experiment is apparent. The candidacy of F has been tested without competition. We do not know how S would have fared without F, or with a different factor G instead of F. Often, the experiment deals with problems so simplified that some such factor G, superior to F, is readily apparent; but the experimenter may then exclude G on the ground that it is "trivial" to tackle P using S with G. In one so-called "historic" experiment, the experimenter ran a slight variation of the single ballot election. He gave his candidate an opponent, but the latter was a paralyzed moron, that is, he chose the worst possible factor G to compete against his proposed F.

Closely related to single ballot elections are what we sometimes call within the group "rat-psychology experiments." Suppose we become interested in the behavior of people. We may have difficulty carrying out certain types of controlled experiments. Therefore we study rats. Very precise results may be obtained, and we may gain considerable insight. Unless that insight, once explicit, can be tested with respect to the larger situation, however, we must be wary of extrapolation. *A rat psychology experiment without a future is a rat psychology experiment*

without a future. Let us present an illustration from our own archives. We collaborated with Friedberg on the second half of a learning machine experiment.[3] Results were obtained for simple problems that could easily be broken down into parts and these parts ordered in terms of difficulty. The results were pertinent for the problems in question, but had little relevance for systems handling larger, less obedient problems. Actually, a rat psychology situation arises not so much from the experiment itself, but rather from the professed motivation and subsequent claims to exercise generality. This is only human, since it is easy to control a small situation and make large claims. Moreover, of course, there is always the problem of selling the experiment. The government, for example, might show little interest in a project to cause a computer to play a good game of zippo; but if the government could be convinced that zippo is a game of strategy and that the project in question might provide insight toward the evolution of a computer system to produce effective strategy decisions for important problems of state, then the government might agree to finance the project.

Much of this methodological fumbling arises from the fact that *it is difficult to make the computer per se an object of scientific curiosity.* The physicist studies by well-established methods a universe that is "there"; and reluctant nature serves not only as a guide, but also as a check upon proposed theories. The mathematician may speculate broadly, but acceptance is generally based upon proof or disproof by methods of known currency. Suppose in studying computers we wish to go beyond mere performance statistics. We propose a certain theory, or point of view. How shall we find confirmation, or disconfirmation? We may set up a computer experiment in which an idealized situation is examined. In order to achieve controls, we simplify greatly. A "rat-psychology" experiment may follow.

On the other hand, we may attempt to resolve the question by purely formal or mathematical studies. Here again there are difficulties. By and large, *the average computer is too vast a system to be considered in purely formal terms.* In a well-known paper[4] Turing showed that any function, computable at all, can be computed by a very economical machine satisfying some very simple requirements. He then showed that certain of these machines are "universal", in the sense that they can compute any computable function. A number of related theorems were obtained, these results being possible largely because of the great economy of the machines studied. To some extent, these theorems apply to actual computers. Generally speaking, however, they clarify only what might be termed extreme "boundary" questions. In fact, we are faced with a dilemma analogous to that mentioned earlier. The typical computer is a well-defined object, but large. If, to achieve manageable mathematics, we hypothesize a greatly simplified machine, our results may not apply in

cases of real interest. For example, suppose we wish to study ways of shortening computer programs. The analogy here between machines in use and Turing machines is remote.

Probably *the greatest understanding of the computer can be obtained from attempted application.* We determine the nature of the beast by trying to use it. In building new machines, however, we continually go from the smaller to the larger. Questions of more than academic interest arise. Suppose we plan to build a computer mightier than any now extant. By the use of redundant, self-checking circuitry, we may very much reduce the probability of machine errors. On the other hand, we increase the complexity of the machine and slow down the operating time. An appropriate point of balance is sought. The stakes are high, since a pronounced error either way would be costly. Formal studies and idealized experiments may prove helpful, but is is doubtful they can settle the issue. Past experience with more limited machines may prove suggestive but nonconclusive. We may be forced to resort to an educated guess.

In fact, a good part of our so-called "hardware" studies have been specifically designed to eliminate guesswork in so far as possible. We have found, for example, that *the logical efficiency of elementary "black boxes" can be equated with their versatility.*[5] Suppose, other factors equal, we wish to select that assortment of basic building blocks that will commonly lead to circuits economical in the number of basic units required. Such "efficiency" is difficult to measure directly. Often, however, the "versatility" of a given assortment can be determined. We may discover, for example, that, with three units of one assortment, we can carry out far more logical operations than with three units of another. Such added versatility will generally be reflected in added efficiency.

Although we have found such efficiency studies profitable, by far the greatest use of logic in hardware studies has been in the development of algorithms for synthesizing and minimizing circuits. The famous paper by Quine is a good example.[6] In this connection, we have felt for some years that *greater emphasis should be placed upon approximating procedures.*[7] Generally speaking, questions dealing with physical reality do not require categorical answers. If we do not seek absolute minimalities, but only near approaches, we stand to gain greatly in the range and efficiency of our methods. It also seems reasonable that *there should be more study of the problem how we design using complicated logical packages.* Anyone who has tried to convince circuit designers that they might profitably use less familiar "black boxes" will appreciate this point.

Of course, since *the basic objective of our entire enterprise is to obtain greater problem-solving capacity,* we need not only better computers, but also more skill in exploiting those we have. Here we realize once again the importance of what might be termed "application studies". This emphasis upon application is closely related to an attidude we enter-

tain toward problems of "artificial intelligence. We all know that computers can manipulate numbers with speed and accuracy. We normally use the computer to solve problems for which we have determined in advance a precise method of solution. This method is translated into computer language, and the machine set to work. Without the computer, the problem might be virtually unsolvable because of the great number of operations required. There are many problems, however, for which we can find in advance no precise method of solution. Nevertheless, in every day life we often manage such problems skillfully and succesfully. Sometimes we do not even know why a given strategy was adopted. Our skill may also improve with practice. Because of such problems and our undoubted success with many of them, it is sometimes argued that the chief problem in artificial intelligence is to cause the machine to solve problems "the way in which people do." We do not deny the value of understanding human problem solving. Nevertheless, for us *the basic problem in artificial intelligence is not to cause the machine to imitate human behavior, but rather to see how to exploit the latent power of the machine in the solution of certain problems.* We have found, for example, in attempting to develop powerful programs for theorem testing and automatic design, that methods quite effective for the computer are inappropriate for us and vice versa. Indeed, the most powerful theorem-testing technique we have found is strongly oriented to the computer;[8] and we have managed design problems, otherwise unsolved, by a relatively simple technique of trial-and-error search, easy on the computer but unsuitable for hand calculation.[9] Of course, it is no secret that "monster" movies still pack in the customers; and so it is only natural that overly anthropomorphic language is sometimes used. What more exiting close to a speech than the blunt, Frankenstein assertion that computers will someday put all theoretical mathematicians out of work!

We should not, however, underestimate the power of the machine. The fact that it can succeed using methods difficult for us is often a source of hope. Consider the theorem-testing project alluded to above. When we reduce semi-intuitive systems to purely formal ones, we both gain and lose. The chief loss is in the added complexity of operation. There are four possible gains. First, a more universal system may be achieved, in the sense that various disciplines related, but independently derived, are obtained from a single source. Second, we are often provided an automatic technique for checking proofs. Third, the formal system itself can serve as a well-defined object of study, so that important metaquestions can be posed and answered. Fourth, the formal system will include new logical techniques for proving theorems. When we survey the actual achievements of logicians in studying mathematics (taken as a semi-intuitive system), we find that the first three sources of gain have proved most bountiful. On the other hand, very few indeed are the mathematical

theorems that have been demonstrated for the first time within a purely formal system. Nevertheless, because of the great inherent power of the computer, we are hopeful that the fourth source of gain can also be exploited.

Although there is advantage in finding the universal ingredient of systems that might reasonably spring from common roots, we doubt the advisability of what might be termed "generic" problem solvers. *Particular advantage must be taken of the particular situation encountered.*[10] Playing chess and testing theorems, for example, differ; and we see little advantage in combining two such diverse programs. In this connection, we tend to regard the computer as an aid to man in his problem solving, rather than as an entity which, once set up, will operate independently. This means that, in an efficient man-machine relationship, there should be frequent interaction of the two.

In closing may we emphasize a point mentioned earlier. Most of the attitudes herein expressed have been developed as hindsight upon our own failures.

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SECTION OF CHEMICAL SCIENCES

MOLECULAR BIOPHYSICS OF DYE-POLYMER COMPLEXES

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A number of organic, cationic dyes form complexes with anionic polymers.[1-5] Striking changes in the optical properties of the dyes accompany complex formation. These same dyes appear to exist as aggregates in concentrated aqueous solutions,[6,7] in detergent micelles, and in tissues stained by the dye.[8,9]

Similarities exist between the optical changes associated with dye aggregation and those accompanying dye-polymer complex formation: in dilute aqueous solution the monomer of a typical aggregating dye, acridine orange (AO), emits in the green (λ_{max} = 533 mμ) and absorbs at λ_{max} = 492m μ (ϵ = 56000). In concentrated solution the aggregated dye emits in the red (λ_{max} = 656 mμ) and absorbs at λ_{max} = 451 mμ[7] with a lowered extinction coefficient (ϵ = 29000). The green monomeric form may be seen throughout cells stained with a dilute AO solution and particularly strongly in the nuclei of living cells (dye binding to deoxyribonucleic acid [DNA]) while the red aggregated form is seen throughout cells stained with more concentrated AO solutions and particularly strongly in the cytoplasm of dead cells (dye aggregation on ribonucleic acid [RNA]).[8,9] Both forms may be seen when AO binds to isolated DNA or RNA in aqueous solution.[8,10,11] With a large excess of either polyanion the monomeric form appears (λ_{max} = 504mμ, ϵ = 55000, green fluorescence). As the ratio of dye to binding groups (phosphates) approaches unity the aggregated form appears (λ_{max} = 464mμ, ϵ = 22-24000, faint red emission). Spectrophotometric titrations indicate that a maximum of one dye can be bound per negatively charged polyanion group.

A strong inference from these and many similar observations is that dyes may aggregate when they form dye-polymer complexes. Many questions as to the molecular-biophysical aspects of this kind of aggregation come to mind. Do the dyes bind indiscriminately to any part of the polymer surface or to specific sites?[12] What is the nature of the binding force(s) that cause the dyes to be bound much more tightly than inorganic ions of like charge? Why does the dye appear to aggregate more strongly on cellular RNA than cellular DNA? How are the dyes spatially related to each other on the polymer? Does aggregation simply involve the binding of a dimer to the surface of the polymer, or does it involve electronic coupling between pairs of dyes, each of which is held fixed to its own binding site?

*This paper, illustrated with slides, was presented at a meeting of the Section on May 2, 1961.

If coupling between dyes held to fixed sites were a valid model then what would be the nature of this coupling? Most types of interactions depend upon the distance and angle between the groups involved.[13,14] If, then, dye aggregation of this type does occur in dye-polymer complexes it should depend upon the intersite spacing of the polymer, that is, dye aggregation should vary with polymer conformation and thus provide a new method for investigating polymer structure. By choosing polymers with a variety of intersite spacings it should be possible to vary the strength of the coupling from "strong" to "weak coupling."[14] By varying the concentration of dye, that is, the dye-polymer ratio in the complex, it should be possible to determine a dimerization constant for dyes aggregating on a regular array of sites. Furthermore, by using a combination of statistical and quantum mechanical methods it should be possible to relate all of the absorption, emission, equilibrium constant, and optical rotation observations in a unified way.

With these considerations in mind we have been studying experimentally the optical properties of dye-polymer complexes while simultaneously developing appropriate statistical treatments of the aggregation of dyes bound to a linear array of sites. In this paper we present a resumé of our efforts in this field, together with quantum mechanical treatments based upon recent theoretical contributions by M. Kasha, W. T. Simpson, W. Rhodes, and I. Tinoco.

In the development that follows, we shall make certain assumptions as to the physical state of the dye-polymer complexes and the nature of the dye-dye and dye-polymer interactions. For example, we shall assume that dyes are bound to specific polymer sites that are held by the primary and secondary structure of the polymer in some kind of regular linear array. Dyes will be assumed to be bound to these sites by electrostatic interactions between the positively charged dyes and negatively charged sites, possibly enhanced by interactions with neighboring sites or by other types of electrical forces. The binding forces will be assumed to orient the dye relative to the sites and the polymer as a whole. Dyes on neighboring sites will be assumed to be sufficiently close to be able to interact with each other in one or more ways. First of all they may interact in such a way as to change their ground-state energies. An important contribution to this effect would arise from dispersion forces between the polarizable π-electron systems. There may also be contributions that have nothing directly to do with dye-dye coupling but only with the change in environment that occurs when a bound-monomer dye surrounded by solvent becomes part of an aggregate in which it is surrounded by other dyes. Ground-state interactions will affect the way in which the dyes are distributed on the sites and, if sufficiently large, they may cause the aggregated dye to be displaced to a certain extent from its equilibrium (monomeric) position on the binding site.

The dyes may also interact so as to alter their excited states. For

example if N dyes on N consecutive sites lie with their molecular planes parallel to each other and perpendicular to their line of centers, interaction may split the first excited state into N-levels of an exciton band,[16] only the highest of which can be reached by light absorption from the ground state. As a result of the formation of this exciton band the aggregate absorbs at shorter wave lengths than the monomer, fluorescence is quenched, and phosphorescence is enhanced.[15] If the group of N-dyes is bound to a helical array of sites then excited state interaction can also lead to optical activity.

We shall now attempt to show how the spectral shift, caused by excited state interactions can be used to compute the fraction of monomeric or dimeric dyes as a function of the dye concentration (dye-polymer ratio) and from this the ground state interaction energy as well as the probability of occurence of any group of filled and empty sites.

Statistical Treatment of the Distribution of Dyes Among Sites

Any given binding site may be either empty (–) or occupied (o) by a single dye molecule. A sequence of N consecutive filled sites is an N-mer, that is, -o- and -oooo- are mono- and tetramers respectively. For any given set of D dyes on P sites there will be a particular distribution of filled sites among the various N-mers. If there are no ground state dye-dye interactions between neighboring filled sites this distribution will be random. If there are ground state interactions and these result in attraction between the neighboring dyes there will be fewer monomers and more of the dimers and higher N-mers. If there are repulsions between neighboring dyes the distribution will be biased in favor of monomers.

Since the effects of dye-dye interaction on the average optical properties of the dye depend both upon the fraction of dyes involved in such interactions (fraction of dimers or higher N-mers) and the size of the aggregates (N) a quantitative analysis of the effects of dye-dye coupling presupposes knowledge of the distribution of dyes among the various N-mers. This distribution can be computed theoretically in terms of either the ground state free energy of interaction of a pair of neighboring dye molecules, ΔF, or a stacking coefficient, K, related to ΔF by the expression $K = e^{-\Delta F/kT}$[5,19]. For example the fraction F_1 of dyes occuring as monomers is given by

$$F_1 = \left(\frac{N_1}{D}\right) = \frac{\Sigma\Sigma K^{D-N}\binom{N_1}{D}\binom{N}{N_1}\binom{D-N-1}{N-N_1-1}\binom{P-D+1}{N}}{\Sigma\Sigma K^{D-N}\binom{N}{N_1}\binom{D-N-1}{N-N_1-1}\binom{P-D+1}{N}} \qquad (1)$$

where N_1 is the number of monomers, N the total number of all N-mers, and

for example, $\binom{N}{N_1} = \frac{N!}{N_1!\,(N-N_1)!}$. K may be thought of as the equilibrium constant for the reversible reaction -o-o- ⇌ -oo--. If there is no ground state interaction then $K = 1.00$.

The dependence of F_1 upon P and D has been studied experimentally for AO bound to a variety of polyanions[5] This has been accomplished by measuring the increase in the monomer absorption band at the band maximum (504 mμ) with increasing P/D ratio. By a process of curve fitting of the observed F_1 and P/D values by the high-polymer limit of Equation **1**, for example,

$$P/D = (1-F^{1/2})^{-1} + (K-1)\,(1-F^{1/2})^{-1}F \qquad (2)$$

it has proved possible to evaluate K for *AO* bound to any given polyion.[5,19]

The range of Ks observed is quite large, from $K = 1.25$ for native DNA to $K = 826$ for polyphosphate and higher for certain acid polysaccharides. The distribution of dyes among various N-mers is thus very sensitive to the polymer to which the dye is bound. There is considerable evidence that the value of K is related to the conformation of the polymer. For example, native DNAs have the same $K = 1.25 \pm 0.07$[20] that increases markedly (→ K = 6.2) upon helix → coil denaturation.[20] AO aggregates more strongly on RNA ($K = 3$) than on DNA.[5] Random coiled poly *A* and poly *U* have $K = 109$ and 161 respectively.[5] However, when they form a multistranded complex, the K value falls to less than 6.[22] Such results are to be expected since the strength of dye-dye coupling ought to depend on the intersite spacing. A fairly general empirical rule is that the more highly ordered polymers have lower K values.

Application of the Statistical Method to Absorption Spectra

Although it is possible to relate the fraction of any N-mer (or, more generally, any given arrangement of filled and empty sites) to P/D for any value of K,[19] these relationships become particularly simple for the random case ($K = 1$). For this reason dye-dye interactions on DNA, which has a K value approaching this limit, are of particular interest. For example, theoretically the fraction F_1 of monomer dyes (-o-) is given by

$$F_1 = (1 - D/P)^2 \qquad (3)$$

for the random case. F_1 is defined experimentally by

$$F_1 = \frac{\epsilon - \epsilon_{P=D}}{\epsilon_{P\gg D} - \epsilon_{P=D}} \qquad (4)$$

where ϵ, $\epsilon_{P=D}$ and $\epsilon_{P\gg D}$ are the molar extinction coefficients at the bound-monomer absorption maximum (504 mμ) of the dye at any P/D, $P=D$, and

$P>>D$ respectively. It is found that for AO/DNA F_1 defined by Equation 4 very nearly satisfies Equation 3.

By fitting F values by the more exact Equation 2 however, it is found that there is actually some nonrandomness ($K = 1.25$) corresponding to a small dye-dye attraction ($\Delta F = -0.065$ kcal./mole dye). The spectral shift accompanying aggregation (504→ 464mμ) corresponds to a 4.8 kcal./mole increase in the energy separation of the ground and excited states. Comparison of this figure with −0.065 kcal./mole for the ground-state free energy decrease leads to the suggestion that the spectral shift results from an increase in energy of the excited state rather than a decrease in the ground state.

Application of the Statistical Method to Optical Rotation

Anomalous optical rotatory dispersion (Cotton effect) has been observed with AO bound to native, helical DNA[23] as well as with acriflavine bound to helical polyglutamic acid[24,25] at low *p*H. The optical activity is related to the helical nature of the polymers since no Cotton effects are observed with randomly coiled, denatured DNA or basic polyglutamate. Cotton effects are observed at several frequencies in both systems. One (designated Cotton effect No. 1) has its inflection point at the band maximum of the aggregated dye (for example, 465 mμ with AO/DNA). The magnitude of Cotton effect No. 1 decreases with increasing P/D as the distribution of dyes shifts from the higher N-mers toward monomers.[23]

Cotton effect No. 2 has an inflection point at the band maximum of the monomeric dye (505 mμ for AO/DNA). Its magnitude is zero at $P=D$ where dyes occur in higher N-mers, passes through a maximum at a $P/D \sim 4$, and decreases to zero at high P/D.

Optical activity originates in electronic coupling between chromophores that occur in an asymmetric pattern. The necessary asymmetry in these two systems is provided by the binding of dyes on a helical array of sites. The required coupling can occur between the dyes and the polymer, especially the nucleotide bases, or between neighboring dyes. The dye-dye coupling that causes the spectral shift is qualitatively sufficient to explain Cotton effect No. 1. Weaker coupling, perhaps between next-nearest neighbor dyes, which would not be sufficiently strong to cause a spectral shift, may be the cause of Cotton effect No. 2. This latter interpretation is supported by an analysis of the dependence of the effect upon P/D.

Assume for the moment that Cotton effect No. 2 results from weak coupling between next-nearest neighbors within an arrangement such as -o-o- (A). For a random distribution the theoretical fraction of dyes occuring in such a configuration is $F_A = k(1-D/P)^3\,(D/P)$ where k is a constant. In general the probability that a dye will occur in configuration i containing m empty and n filled sites is given by

$$F_i = ki(1-D/P)^m\,(D/P)^{n-1} \qquad (5)$$

The fact that an equation of this form does fit the experimental AO/DNA rotation data with reasonable accuracy,[23] suggests that coupling in an arrangement of 3 empty and 2 filled sites such as (*A*) does contribute appreciably to Cotton effect No. 2. In general the observed rotation will consists of a weighted average of contributions from not just one but a variety of arrangements such as (*A*). Therefore, close fit of rotation data by the probability curve for a single arrangement may be fortuitous. In such cases relatively close fit may be obtained with more than one arrangement. For example the arrangement -o-o-o-- (*B*) has a probability curve $F_B = k(1-D/P)^5 (D/P)^2$ which fits the rotation data for AO/DNA about as well as F_A.

In the acriflavine/polyglutamate system, where the distribution of dye among *N*-mers is far from random (high *K*), Cotton effect No. 2 reaches its maximum value at much higher *P/D* ratios than in the AO/DNA system. Recent unpublished work in these laboratories by D. M. Neville has shown that the maximum value of rotation of Cotton effect No. 2 in the AO/ribonucleic acid system (intermediate *K*) occurs at intermediate *P/D* ratios.

By varying *P/D* it is thus apparently possible to change continuously from "strong coupling"[14] (Cotton effect No. 1, spectral shift) to "weak coupling"[14] (Cotton effect No. 2, no spectral shift), to no coupling (no Cotton effect, no spectral shift). The rate with which these changes occur with increasing *P/D*, however, depends upon the degree to which ground state interactions ($K, \Delta F$) affect the distribution of dyes among *N*-mers.

Application of the Statistical Method to Fluorescence

The green emission of AO in dilute aqueous solution ($2 \times 10^{-5} M$) is quenched ($\sim$ 96 per cent) when the dye forms a 1:1 complex with DNA.[26] This emission reappears as the P/D ratio of the complex increases and ultimately reaches an intensity several times that of the free dye at the same concentration. However, emission intensity increases with *P/D* less rapidly than the monomer absorption intensity, that is, $n = 1$, $m = 2$ for absorption and $n = 1$, $m > 2$ for emission (Equation 5). The fact that it requires more than one empty site around each dye to prevent quenching of emission ($m > 2$) leads to the suggestion that, as was observed in the case of optical rotation, dye-dye coupling leading to fluorescence quenching, may occur between weak-coupled next-nearest and more distant neighbors[27] as well as between strong-coupled nearest neighbors. Quenching of fluorescence in strong-coupled dye aggregates has been ascribed to enhanced intersystem crossing (singlet→triplet) and to the fact that emission from the lower singlet energy levels of the exciton band is forbidden.[18]

Quantum Mechanical Treatment of Aggregation

The examples above illustrate how the statistical method may be applied to absorption, optical rotation, and fluorescence changes in order to elucidate the relationships between the dyes in the interacting units of

filled and empty sites. However, to compute the magnitude of any of these changes in terms if the molecular properties of the dyes a quantum mechanical treatment is required. Although detailed quantum mechanical treatments for these systems are available,[17,18] certain useful results may be obtained by the application of simpler treatments.

Dyes bound from a monomeric dye solution may be either monomeric (-o-) or dimeric (-oo-) on the polymer depending on whether neighboring sites are empty or filled (FIGURE 1). As a result of binding the energy levels of the ground and excited states will change although not necessarily by the same amount. For example, the excited state may undergo additional stabilization because of dipole-polarizability interactions with the DNA nucleotides, leading to a red shift such as is actually observed with many dye-polynucleotides systems[28] ($\nu' - \nu = -480$ cm^{-1} for AO/DNA).

For strong-coupled, dimeric dye the excited state is split into a two-fold exciton band. Two geometric arrangements in the dimer are of particular interest: card-pack stacking (molecular planes and/or transition moments parallel to each other and perpendicular to their line of centers) and head-to-tail (colinear). Actually it is the relative orientations of the transition moments that enter into the calculations but these are generally related to the molecular orientation in a relatively simple manner, for example, the transition moment for the longest wave-length transition may be in-plane and directed along the long axis of the molecule. For card-pack stacking the transition moments are in phase (↑↑) in the upper state and out of phase in the lower state (↑↓). For head-to-tail ordering the reverse is true. Light absorption is allowed only to the state where the moments are in phase so that card- pack stacking causes a blue-shift and head-to-tail ordering a red-shift.[13,16]

The magnitude of the exciton splitting can be readily calculated if only the transition dipole-dipole interaction is considered, and permanent dipole interactions, mixing higher states into the wave functions for these states *etc.*, are neglected. The equation of Levinson *et al.*[13] predicts that

$$\Delta\nu = \nu'' - \nu' = \frac{M^2}{R^3} \approx 1.16 \times 10^{-3} \frac{q^2}{R^3} \qquad (6)$$

where M = bound-monomer transition moment, $q^2 = -1.1 \times 10^{-19} \int \epsilon d\log_{10}\lambda$ and R = interplane spacing. Taking $q = 1.68 \times 10^{-8}$ cm, for monomeric DNA-bound AO[20] and R as the distance between successive P atoms in DNA (6.5×10^{-8} cm)[29] Equation 6 predicts a blue-shift of 1180 cm.$^{-1}$ for an AO card pack dimer on DNA. In this treatment higher N-mers would be expected to show increased splittings approaching a limit of $2 \times 1180 = 2360$ cm.$^{-1}$ as $N \to \infty$. In a 1:1 complex with DNA the observed shift is 1700 cm.$^{-1}$ corresponding to an average stack height of 3 ($1180\sqrt{2} = 1670$ cm.$^{-1}$).

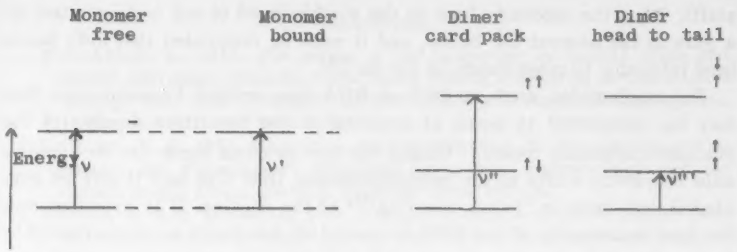

FIGURE 1.

The actual system is of course much more complex than the model. For example, pairs of AO molecules bound to helically ordered sites probably do not lie with their transition moments parallel. Furthermore the selection rules for helical stacks are more complex than was assumed in the calculation.[30] The agreement between the observed and calculated splittings is therefore better than what might be expected in view of the approximations made in the calculation.

The spectral shift for aggregation in solution in the absence of polymer is 1840 cm.$^{-1}$.[7] Agreement between this value and that for the 1:1 AO/DNA complex was originally a strong argument for interpreting the polymer-bound dye spectrum in terms of aggregation. However, this agreement may result from a compensation between the effects of having taller stacks in the DNA-bound dye and a smaller interplane spacing in the free aggregate.

Using this same model it is possible to predict the effect of aggregation upon the absorption intensity. If the only interaction to be considered is that between the transition dipoles that leads to the exciton splitting, there should be no hypochromism, that is, no decrease in integrated absorption intensity or oscillator strength, $f = 4.32 \times 10^{-9} \int \epsilon d\nu$.[13,31] There could of course occur a decrease in the extinction coefficient, ϵ, because of the shift to higher frequencies upon aggregation. There is, however, a decrease in integrated intensity (20 per cent) as well as ϵ when AO aggregates either on DNA ($f_{\text{monomer}} = 0.51$; $f_{\text{aggregate}} = 0.40$) or in solution. ($f_{\text{monomer}} = 0.63$; $f_{\text{dimer}} = 0.50$).[7] This loss of intensity may be interpreted in terms of interactions of the transition moment of the visible band with those of transitions to higher states, which lead to the lending of intensity to these higher energy transitions.

The nearest transitions in AO occur in the ultraviolet at 290, 270, and 230 mμ. Intensity changes in AO in this region of the spectrum are more easily followed when AO is bound to polymers that are themselves transparent in this region, for example, polyphosphate or heparin. In these systems aggregation is even more pronounced, since the blue shift is to 450 mμ and the extinction falls to less than 20000 (58 per cent decrease).[32] However the ultraviolet bands also show a decrease in extinction (35 per cent)[32] together with little change in shape or position of the band (<4 mμ

shift). Thus the intensity loss in the visible band is not compensated by a gain in the nearest UV bands, and it must be concluded that both bands lend intensity to other bands in the far UV.

Polynucleotides such as DNA or RNA also exhibit hypochromism that may be interpreted in terms of coupling of the transition dipoles of the stacked nucleotide bases.[17] Unlike the dye systems there are no appreciable frequency shifts in the polynucleotides; from this fact it may be concluded that there is "weak coupling"[14] of the dipoles. It is expected that the loss in intensity of the 2600 Å nucleotide band will be compensated by an increase in higher transitions, although not necessarily the nearest one.

Combination of Statistical and Quantum Mechanical Methods

The examples cited above indicate some of the ways in which optical data on dye-polymer complexes in conjunction with statistical and quantum methods may be helpful in answering questions about the dye-polymer and dye-dye interactions. For example, the success of a statistical method based on specific-site binding provides further support for this type of binding.

Much remains to be done. Considering, for example, just the theoretical treatment of optical rotatory dispersion, logically the next steps to take would be (1) to determine the coordinates of the dyes relative to the DNA structure by some suitable method such as X-ray diffraction (as recently attempted by Lerman[13]), (2) to compute the transition moment directions for the first and several higher transitions, (3) to use strong coupling theory[18] to compute the rotation for each arrangement of dyes on sites (for example, *A* or *B*), (4) to weight each configuration by its probability of occurence, and (5) to sum up over-all configurations that contribute to the rotation. Even such detailed calculations will involve seriously limiting approximations. For example, transition monopole or dipole orientations computed by standard molecular orbital methods are at best approximations. Furthermore, observed rotations are small differences obtained by summing many terms of large magnitude and of opposite signs so that small variations or uncertainties in the numerical values of the parameters used in the calculations may result in large changes in the computed total rotation[18].

However, by continued development along these lines it may be possible to obtain a combined statistical and quantum mechanical model that will encompass all of the observed effects of dye-dye coupling with one (or a small number) of interaction parameters. Once this is accomplished it may well prove possible to use dyes to provide detailed information about intersite spacings in polymers.

Acknowledgments

I express my sincere appreciation to M. Kasha, W. T. Simpson, I. Tinoco, W. Rhodes, and H. DeVoe for many helpful discussions on the quantum mechanical aspects of this problem.

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CONFERENCES HELD

SECTION OF BIOLOGICAL AND MEDICAL SCIENCES

UNSOLVED PROBLEMS OF THIAMINE

COMMEMORATING THE 25TH ANNIVERSARY OF THE THIAMINE SYNTHESIS BY ROBERT R. WILLIAMS AND COLLABORATORS

Thursday, September 21 and
Friday, September 22, 1961

Conference Chairman: Heinz M. Wuest
Sloan-Kettering Institute for Cancer Research, New York, N.Y.

THURSDAY, SEPTEMBER 21, 1961

Session Chairman: W. H. Sebrell, Jr.
Columbia University, New York, N.Y.

9:00 A.M.–
Greetings from the Academy – Frederick Y. Wiselogle, President, The New York Academy of Sciences; New York, N.Y.; The Squibb Institute for Medical Research, New Brunswick, N.J.

"History and Present Status of Thiamine" – Heinz M. Wuest, Sloan-Kettering Institute for Cancer Research, New York, N.Y.

"Condensation of Thiamine with Aldehydes" – James Sprague, Merck, Sharp and Dohme, Rahway, N.J.

"Antimetabolites of Thiamine" – Edward Rogers, Merck and Co., Rahway, N.J.

"Absorption Spectra and Structure of Thiamine at *p*H 1-14" – Heinz M. Wuest, J. P. Ruckstuhl and Naishun Yung, Sloan-Kettering Institute for Cancer Research, New York, N.Y.

"The Synthesis of S-Acylthiamine Derivatives and their Stability" – Taizo Matsukawa, Shojiro Yurugi and Yoshikazu Oka, Research Laboratories, Takeda Chemical Industries, Ltd., Osaka, Japan.

COCARBOXYLASE: MODE OF ACTION, REACTION MECHANISM AND ROLE OF THE ACTIVE ACETATE

Session Chairman: Severo Ochoa
New York University, New York, N.Y.

2:00 P.M.–
Opening remarks – Severo Ochoa, New York University, New York, N.Y.

"Mechanism of Thiamine Action: Predictions from Model Experiments" R. Breslow, Columbia University, New York, N.Y.

"Active Forms of Acetaldehyde, Pyruvate, and Glycolic Aldehyde" – Helmut Holzer, University of Freiburg, Freiburg, Germany

"Mechanism of Action of Thiamine Diphosphate in Enzymic Reactions" – L. O. Krampitz, Westem Reserve University, Cleveland, Ohio

"Mechanism of Enzymatic Formation of Thiamine from the Two Moieties" – Gene M. Brown, Massachusetts Institute of Technology, Cambridge, Mass.

"Thiamine Phosphate PyroPhosphorylase from Baker's Yeast" – I. G. Leder, National Institute for Arthritis and Metabolic Diseases, Public Health Service, Bethesda, Md.

"The Possible Biologic Role for the Tricyclic Form of Thiamine" – D. E. Metzler, Department of Biochemistry, Iowa State College, Ames, Iowa.

FRIDAY, SEPTEMBER 22, 1961

Session Chairman: Randolph Major
University of Virginia, Charlottesville, Va.

9:00 A.M.–
"The Role of Thiamine in Neurophysiology" – Alexander von Muralt, University of Berne, Berne, Switzerland

"The Occurrence of Thiamine Metabolites in Rat Liver after Administration of 35S-Labeled Thiamine" – O. Wiss and G. Brubacher, Hoffman-La Roche, Ltd., Basel, Switzerland.

"Thiamine in Germfree Animals: Effect of the Intestinal Microflora on Thiamine Metabolism" B. Wostman, University of Notre Dame, Lobund Institute, Notre Dame, Ind.

"Erythrocyte Transketolase in Early Thiamine Deficiency" – Myron Brin, Syracuse University, Syracuse, N.Y.

"Human Requirements of Thiamine as Related to Other B Vitamins" – Helen G. Oldham, Human Nutrition Research Division, U. S. Department of Agriculture, Washington, D. C.

"The Therapeutic Use of Thiamine in Diseases not Related to Beriberi" – Gerhard Zbinden, Hoffmann-La Roche, Inc., Nutley, N.J.

Session Chairman: C. Glen King
Columbia University, New York, N.Y.

2:00 P.M.–
Opening Remarks – C. Glen King, Columbia University, New York, N.Y.

"Clinical Evaluation of Thiamine Deficiency" – W. H. Sebrell, Jr., Columbia University, New York, N.Y.

"Experience in the Etiology and Prevention of Thiamine Deficiency in the Philippines" – Juan Salcedo, Jr., University of the East, Quezon City, Republic of the Philippines.

"Relationships of Beriberi and Thiamine in the Rice Diet and Infantile Beri-beri" – A. Sreenivasan, Central Food Technological Research Institute, Mysore, India.

"Thiamine Enrichment in the United States" – William Bradley, American Institute of Baking, Chicago, Ill.

"Thiamine Enrichment Outside the United States" – George Parman, Hoffman-La Roche, Inc., Nutley, N.J.

Closing Remarks – Heinz M. Wuest, Sloan-Kettering Institute for Cancer Research, New York, N.Y.

SECTION OF BIOLOGICAL AND MEDICAL SCIENCES

Charles Noback
Chairman

Preston L. Perlman
Vice-Chairman

SECTION OF BIOLOGICAL AND MEDICAL SCIENCES

AND DIVISION OF INSTRUMENTATION

SCANNING TECHNIQUES IN BIOLOGY AND MEDICINE

Thursday, October 5 and
Friday October 6, 1961

Conference Chairman: P. O'B. Montgomery
The University of Texas Southwestern Medical School
Dallas, Texas

THURSDAY, OCTOBER 5, 1961

Session Chairman: P. O'B. Montgomery
The University of Texas Southwestern Medical School, Dallas, Texas

9:00 A.M.–
Greetings from the Academy – Andres Ferrari, Chairman, Division of Instrumentation, The New York Academy of Sciences, New York, N.Y. The Technicon Corporation, Chauncey, N.Y.

Introductory Remarks – P. O'B. Montgomery, The University of Texas Southwestern Medical School, Dallas, Texas.

"Microsurgery and Visible Light Television" – M. J. Kopac, Graduate School of Arts and Sciences, New York University, New York, N.Y.

"Cytochemical Studies and Quantitative Television Fluorescence and Absorption Spectroscopy" – Charles N. Loeser and Seymour S. West, Department of Anatomy, School of Medicine, Western Reserve University, Cleveland, Ohio.

"Ultraviolet Television Microscopy" – Robert G. Neuhauser, RCA Electron Tube Division, Television Camera Tube Development, Lancaster, Pa.

"Ultraviolet Color-Translating Television Microscopy" – V. K. Zworykin and Carl Berkley, The Rockefeller Institute, New York, N.Y.

Session Chairman: V. K. Zworykin
The Rockefeller Institute, New York, N.Y.

2:00 P.M.–
"Quantitative Cytological Measurements by Flying Spot Scanning Methods" – Joseph G. Hoffman, Roswell Park Memorial Institute, Buffalo, N.Y.

"Television Microscopy – Visible and Ultraviolet" – Leslie E. Flory, David Sarnoff Research Center, Princeton, N.J.

"Ultraviolet Flying Spot Irradiation Combined with Visible Light Phase Contrast Television Microscopy" – W. A. Bonner, The University of Texas Southwestern Medical School, Dallas, Texas.

"Development of the Vibrating Mirror Flying Spot Microscope for Ultraviolet Spectrophotometry" – Jerome J. Freed and J. Engle, The Institute for Cancer Research, Fox Chase, Philadelphia, Pa.

FRIDAY, OCTOBER 6, 1961

Session Chairman: M. J. Kopac
Graduate School of Arts and Science, New York University, New York, N.Y.

9:00 A.M.–
"Microfluorimetry and Microspectrophotometry of Respiratory Enzymes" – Britton Chance, The Johnson Foundation for Medical Physics, Philadelphia, Pa.

"Scanning Microscopy Techniques for High Resolution Quantitative Cytochemistry" – T. Caspersson, Karolinska Institute, Stockholm, Sweden.

"Scanning Electron and X-ray Microscopy" – V. E. Cosslett, Cavendish Laboratory, Cambridge, England.

Session Chairman: T. Caspersson
Karolinska Institute, Stockholm, Sweden

2:00 P.M.–
"Simultaneous Ultraviolet and Visible Light Flying Spot Television Microscopy" – P. O'B. Montgomery, The University of Texas Southwestern Medical School, Dallas, Texas.

"Exfoliated Cell Studies and the Cytoanalyzer" – Elaine G. Diacumakos and Emerson Day, Sloan-Kettering Institute for Cancer Research, New York, N.Y.

"Flying Spot Interference Microscopy" – L. L. Hundley, The University of Texas Southwestern Medical School, Dallas, Texas.

"Size and Shape Determination in Scanning Microscopy" – Walter E. Tolles and H. P. Mansberg, Airborne Instruments Laboratory, Deer Park, N.Y.

SECTION OF BIOLOGICAL AND MEDICAL SCIENCES

Charles Noback
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DIVISION OF INSTRUMENTATION

Andres Ferrari
Chairman

Walter E. Tolles
Vice-Chairman

SECTION OF BIOLOGICAL AND MEDICAL SCIENCES

FIFTH INTERNATIONAL PIGMENT CELL CONFERENCE

Wednesday, October 11
Thursday, October 12
Friday, October 13 and
Saturday, October 14, 1961

Conference Cochairmen

Vernon Riley, Sloan-Kettering Institute for Cancer Research, Rye, N. Y.
and
Joseph G. Fortner, Memorial Hospital and Sloan-Kettering Institute for Cancer Research, New York, N. Y.

WEDNESDAY, OCTOBER 11, 1961

A. ABNORMAL AND MALIGNANT MELANOCYTES IN HUMANS: THEIR OCCURRENCE, RECOGNITION AND SIGNIFICANCE

Session Chairman: Ronald Raven
Royal Cancer Hospital, London, England

9:00 A.M. –
Welcoming Remarks - John R. Heller, President, Memorial Sloan-Kettering Cancer Center, New York, N. Y.

"Epidemiology of Melanoma" - Eleanor J. Macdonald, M. D. Anderson Hospital and Tumor Institute, Houston, Texas.

"Ultrasound Diagnosis in Intraocular Melanoma" - Arvo Oksala, University Eye Clinic, Keskussairaala, Turku, Finland.

"Melanoma Cells in the Peripheral Blood" - Sam Seal, Arthur Levin, and Joseph G. Fortner, Memorial Sloan-Kettering Cancer Center, New York, N.Y.

"Juvenile Melanomas of Children and Adults and Melanocarcinomas of Children" - Arthur C. Allen, The Jewish Hospital of Brooklyn, Brooklyn, N. Y.

"Effect of Topical Hormones and Other Dermatological Therapy on Melanin Pigment" - Herbert J. Spoor, Cornell University Medical School, New York, N. Y.

"Induced Alterations of Vitiliginous Skin" - Robert Stolar, Washington, D. C.

"Pigmentary Disorders of the Skin and their Relation to Internal Tumors" - Helen O. Curth, College of Physicians and Surgeons, New York, N. Y.

"Observations on Human Melanoma Cells in Tissue Culture" (Film) - George G. Rose, Hermann Hospital, Houston, Texas.

B. THE MALIGNANT HUMAN MELANOCYTE: ITS CLINICAL CONSEQUENCE AND CONTROL PROBLEMS

Session Chairman: George T. Pack
Memorial Hospital, New York, N. Y.

2:00 P.M. –

"The Role of Natural Resistance in the Prognosis of Human Melanoma" Laurens P. White, Childrens Cancer Research Foundation, Boston, Mass.

"The Clinical Significance of Regional Satellitosis" - Leonard Triedman and Gordon McNeer, Memorial Hospital, New York, N. Y.

"Radiation Therapy of Primary and Metastatic Melanoma" - Werner Hellriegel, Universtäts des Röentgen Institut, Frankfurt, Germany.

"Perfusion Techniques in Treatment of Malignant Melanoma" - John S. Stehlin, Jr. and R. Lee Clark, M. D. Anderson Hospital and Tumor Institute, Houston, Texas.

"Clinicopathological Aspects of Malignant Melanoma" - Ronald Raven, Royal Cancer Hospital, London, England

Panel Discussion

TREATMENT OF MELANOMA

Chairman: Gordon McNeer
Memorial Center, New York, N. Y.

Robert J. Booher:	Memorial Hospital, New York, N. Y.
R. D. Brasfield:	Memorial Hospital, New York, N. Y.
Joseph G. Fortner:	Memorial Hospital Research Center, N. Y.
Thomas Hall:	Lemuel Shattuck Hospital, Boston, Mass.
Theodore R. Miller:	Memorial Hospital, New York, N. Y.
George T. Pack:	Memorial Hospital, New York, N. Y.
Ronald Raven:	Royal Cancer Hospital, London, England
John S. Stehlin, Jr.:	M. D. Anderson Hospital & Tumor Institute, Houston, Texas.

Steven Gumport: New York University-Bellevue Medical Center, New York, N. Y.

THURSDAY, OCTOBER 12, 1961

9:00 A.M. –

Greetings from the Academy - Charles R. Noback, Chairman, Section of Biological and Medical Sciences, The New York Academy of Sciences, New York, N. Y.; College of Physicians and Surgeons, Columbia University, New York, N. Y.

Opening Remarks - Vernon Riley, Sloan-Kettering Institute for Cancer Research, Rye, N. Y.

A. NATURE, RESPONSE, AND INDUCTION OF MELANOCYTES

Session Chairman: R. D. Passey
Chester Beatty Research Institute, London, England

"A Histologic Study of the Dermoepidermal Junction in Clinically Intradermal Nevi Employing Serial Sections" - Alfred W. Kopf and Rafael Andrade, New York University Bellevue Medical Center, New York, N. Y.

"Light and Electron Microscopic Studies on Normal and Abnormal Human Epidermis with Reference to the Relation Between Langerhans Cells and Melanocytes" - A. S. Breathnack, St. Mary's Hospital, M. S. C. Birbeck and J. D. Everall, Chester Beatty Research Institute, London, England.

"Amelanotic Melanocytes in the Outer Sheath of the Human Hair Follicle and Their Role in the Repigmentation of Regenerated Epidermis" - Renato G. Staricco, Wayne State University, Detroit, Mich.

"Benign and Precancerous Nonnevoid Melanocytic Tumors" - Herman Pinkus and Yutaka Mishima, Wayne State University, Detroit, Mich.

"The Effect of Carcinogens on Melanocytes" - George Szabo, Harvard Medical School, Massachusetts General Hospital, Boston, Mass.

"Carcinogen-Induced Melanotic Tumors in the Syrian Hamster" - Henry Rappaport and Philippe Shubik, Chicago Medical School, Chicago, Ill.

"Effects of Sex and Castration on the Malignant Melanoma of the Hamster" J. C. Rosenberg, and C. Assimacopoulos, University of Minnesota Hospitals, Minneapolis, Minn., and S. A. Rosenberg, Johns Hopkins University Baltimore, Md.

"Cytological Analysis of the S91 Mouse Melanoma in Tissue Culture" - Adolph E. Sloboda, Lederle Laboratories, Pearl River, N. Y., and M. J. Kopac, New York University, New York, N. Y.

"Chemotherapy of Harding-Passey Melanoma" - Kanematsu Sugiura, Sloan-Kettering Institute for Cancer Research, Rye, N. Y. (Read by title.)

B. NATURE, RESPONSE, AND INDUCTION OF MELANOCYTES, (Cont.)

Session Chairman: Stephen Rothman
University of Chicago, Argonne Cancer Research Hospital
Chicago, Ill.

2:00 P.M. –

"Further Studies on the Phenomenon of Pigment Spread in Guinea Pig's Skin" - Willys K. Silvers and R. E. Billingham, Wistar Institute, Philadelphia, Pa.

"Studies on Radiation-Induced Tanning of Skin" - Walter C. Quevedo, Jr., Brown University, Providence, R. I., and Jean A. Smith, Roswell Park Memorial Institute, Springville, N. Y.

"Evidence for Indirect Effect of Radiations of Heavy Ions and Electrons on Hair Depigmentation" - Herman B. Chase, William E. Straile, and Claudette Arsenault, Brown University, Providence, R. I.

"The Nature of the Effect of X Irradiation in Depigmentation" - Jack Cohen, University of Birmingham, Birmingham, England.

"Behavior of Retinal Pigment Cells in Heterotypic Cell Aggregates" - J. P. Trinkaus, Yale University, New Haven, Conn.

"Effects of Pigment on Bovine Ocular Squamous Carcinoma" - David E. Anderson, M.D. Anderson Hospital and Tumor Institute, Houston, Texas.

"Pigment Cells of the Mammalian Iris" - A. J. Tousimis, George Washington University Medical School, Washington, D. C.

"Prolongation of Survival in Ocular Malignant Melanoma of the Hamster by Removal of the Eye" - Robert P. Burns, Fredrick Fraunfelder and Alvin Klass, University of Oregon Medical School, Portland, Ore.

"Some Considerations on the Tissue Culture of Uveal Melanomas" - Y. Robert Barishak, Istanbul, Turkey - Discussant.

"Morphogenesis of Pigment Cells in the Connective Tissues of the Pet Mouse" - Willie M. Reams, Jr., Louisiana State University, Baton Rouge, La. (Read by title.)

"Pigmented Intraocular Tumors in Animals" - C. N. Barron, University of Pennsylvania and Smith Kline and French Laboratories, Philadelphia, Pa. (Read by title.)

Session Chairman: M. J. Kopac
Graduate School of Arts and Science, New York University,
New York, N. Y.

7:30 P.M. —

Symposium: C. MELANIN GRANULES, THEIR NATURE AND ORIGIN

"The Melanosome, a Distinct Entity" - M. Seiji, T. B. Fitzpatrick, and K. Shimao, Harvard Medical School, Massachusetts General Hospital, Boston, Mass.

"The Ontogenic Status of Melanin Granules" - Mark Woods, Dean Burk, and Jehu Hunter, National Cancer Institute, Bethesda, Md.

"Electron Microscopy of Melanocytes" - M. S. C. Birbeck, Chester Beatty Research Institute, London, England.

"Electron Microscopic Studies on the Subcellular Origin and Ultrastructure of Melanin Granules in Mammalian Melanomas" - S. R. Wellings and Benjamin V. Siegel, University of Oregon Medical School, Portland, Ore.

"Enzymic and Other Similarities of Pigmented Granules and Mitochondria" - Herman DuBuy, National Cancer Institute, Bethesda, Md.

"The Fine Structure of Melanin Granules in Normal and Pathological Tissues" - Frank H. Moyer, Jr., Johns Hopkins University Medical School, Baltimore, Md.

"On the Ultrastructure of Unmelanized Pigment Cells in Induced Melanogenesis" - Yutaka Mishima and Alden V. Loud, Wayne State University College of Medicine and Detroit Institute of Cancer Research, Detroit, Mich.

Discussant - A. J. Dalton, National Cancer Institute, Bethesda, Md.

Discussant - H. Fernandez-Moran, Massachusetts General Hospital, Boston, Mass.

FRIDAY, OCTOBER 13, 1961

A. HORMONES IN PIGMENT CELL MECHANISMS

Session Chairman: Aaron B. Lerner
Yale University School of Medicine, New Haven, Conn.

9:00 A.M. —

"Clinical Effects and Mechanisms of Action of the Melanocyte-Stimulating Hormones" - Joseph S. McGuire, Yale University School of Medicine, New Haven, Conn.

B. MELANOCYTE GENETICS: CLASSICAL AND NEOCLASSICAL

Session Chairman: R. E. Billingham
Wistar Institute, Philadelphia, Pa.

2:00 P.M. –

"The Relation of Race and Complexion to the Incidence of Moles and Melanomas" - George T. Pack and Jeff Davis, Memorial Hospital, New York, N. Y.

"The Value of Urinary MSH Assays as an Index of Pituitary Function in Women" - Bruno C. G. Dahlberg, Women's Clinic, Malmö, Sweden.

"Melanocyte-Stimulating Hormone, a Clinical and Laboratory Study" - B. W. McGuinness, Nicholas Research Institute, Slough, Buckinghamshire, England.

"Species Differences and Structural Requirement for Melanocyte-Stimulating Activity of Melanocyte Stimulating Hormones" - T. H. Lee, Yale University, New Haven, Conn.

"Melanophore Stimulating Hormones in Vertebrates" - A. C. J. Burgers, University of Utrecht, Utrecht, Netherlands.

"Endocrine Control of Pigmentation" - Walter Chavin, Wayne State University, Detroit, Mich.

"Reflectance Responses of Frogs to Melanophore Hormone" - Robert S. Teague, University of Alabama Medical Center, Birmingham, Ala.

"The Effects of Temperature on the Response to Melanocyte-Stimulating Hormone" - Griff T. Ross and William D. Odell, National Cancer Institute, Bethesda, Md.

"Some Physiological Genetic Aspects of Mammalian Melanogenesis" - Morris Foster, University of Michigan, Ann Arbor, Mich.

"Studies on the Mechanism of ACTH-Induced Melanocyte Formation in Goldfish" - Ki Han Kim, T. T. Tchen, and Funan Hu, Wayne State University, Detroit, Mich.

"Agouti Melanocytes *in Situ* and *in Vitro*" - Gunter Cleffmann, Zoologisches Institut, Marburg an der Lahn, Germany.

"Enzymatic Determination of Transmissible Replicating Factors Associated with Mouse Melanomas" - Vernon Riley, Sloan-Kettering Institute for Cancer Research, Rye, N. Y.

"Utilization of an Induced *Drosophila* Melanoma in the Study of Mammalian Neoplasia" - R. Kassel, L. Burton, and F. Friedman, St. Vincent's Hospital, New York, N. Y.

"Induced Genetic Change in *Drosophila melanogaster* by Injected Extracts of Neoplastic Flies, Mice, and Humans" - Morris H. Harnly, New York University, New York, N. Y.

"Genetic Regulation of Dopa Oxidase Activity in *Drosophila*" - Herman W. Lewis, Michigan State University, Rochester, Mich.

SATURDAY, OCTOBER 14, 1961

A. MOLECULAR AND MACROMOLECULAR ASPECTS OF MELANOGENESIS

Session Chairman: G. A. Swan
University of Durham, King's College
New Castle-upon-Tyne, England

9:00 A.M.

"Tyrosinase as a Model of the Genetic Control of Protein Structure" - Allen S. Fox and Jean B. Burnett, Michigan State University, East Lansing, Mich.

"Aerobic and Anaerobic Carbohydrate Utilization in Normal and Melanotic Fish Pigment Cells" - Douglas G. Humm and Jane Humm, University of North Carolina, Chapel Hill, N. C.

"Glycolysis by Subcellular Melanoma Fractions and Effects of Insulin and Endotoxin" - Karl Giger, National Cancer Institute, Bethesda, Md.

"Cytotoxicity of Melanin Precursors" - Paul Hochstein and Gerald Cohen, Columbia University, New York, N. Y.

"Melanogenic Enzyme Activity in the Gene-Induced Tumors of Xiphophorin Fishes" - Sylvia S. Greenberg, New York Zoological Society, New York, N. Y., and M. J. Kopac, New York University, New York, N. Y.

"Cholinesterase Studies of the Dermal Nevus and Pigmented Tumors" - R. K. Winkelmann, Mayo Clinic, Rochester, Minn.

"On the Pathway of the Catechol-Tyrosinase Reaction" - C. R. Dawson and W. B, Tarpley, College of Physicians and Surgeons, Columbia University, New York, N. Y.

B. MOLECULAR AND MACROMOLECULAR ASPECTS OF MELANOGENESIS

Session Chairman: C. R. Dawson
College of Physicians and Surgeons, New York, N. Y.

2:00 P.M. —

"Chemical and Autoradiographic Analysis of Tyrosinase Activity in

Melanoma and Related Lesions" - J. P. Chang, W. O. Russell, J. S. Stehlin, Jr., and J. Leslie Smith, Jr., M. D. Anderson Hospital and Tumor Institute, Houston, Texas.

"Tyrosinase, Copper, and the Kinetic Stability of Oxygen" - Harold J. Bright, Brian J. B. Wood, and Lloyd L. Ingraham, University of California, Davis, Calif.

"The Relation between Chromatophores and Pterin Compounds" - Tadao Hama, Keio University, Yokohama, Japan.

"Chromatographic Analysis of Urinary Melanin Pigment" - E. Ghislandi, Clinica del Lavoro dell' Università di Milano, Milan, Italy.

"Site of Action of Chemical Agents on Fish Melanophore with Special Reference to Electrophoretic Theory of Pigment Migration" - Haruo Kinosita, University of Tokyo, Tokyo, Japan.

"Chemical Structure of Melanins" - G. A. Swan, University of Durham, King's College, New Castle-upon-Tyne, England.

"Tyrosine Metabolism in Insects" - P. Brunet, Oxford University, Oxford, England.

"Responses of Cultured Melanophores to the Synthetic Hormones (∝) MSH, Melatonin and Epinephrine" - Ronald R. Novales, Northwestern University, Evanston, Ill. (Read by title.)

SECTION OF BIOLOGICAL AND MEDICAL SCIENCES

Charles Noback
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THE NEW YORK ACADEMY OF SCIENCES

THE MANAGEMENT OF PEPTIC ULCER

Monday, October 16 and
Tuesday, October 17, 1961

Conference Chairman: David C. H. Sun
Mt. Alto Veterans Administration Hospital and
The George Washington University
Washington, D.C.

MONDAY, OCTOBER 16, 1961

Session Chairman: Franklin Hollander
Mt. Sinai Hospital, New York, N. Y.

9:00 A.M. —

Greetings from the Academy - Charles Noback, Chairman, Section of Biological and Medical Sciences, The New York Academy of Sciences, New York, N. Y.; College of Physicians and Surgeons, Columbia University, New York, N. Y.

Opening Remarks - David C. H. Sun, Mt. Alto Veterans Administration Hospital and The George Washington University, Washington, D. C.

"Recent Advances in the Physiology of Gastric Secretion" - Franklin Hollander, Mt. Sinai Hospital, New York, N. Y.

"The Fine Structure of the Oxyntic Cell in Relation to Functional Activity in the Stomach" - Albert W. Sedar, Jefferson Medical College, Philadelphia, Pa.

"The Role of Histamine in Gastric HCl Secretion" - T. M. Lin, Eli Lilly Research Laboratories, Indianapolis, Ind.

"Duodenal Mechanisms for Inhibition of Gastric Secretion" - Rene Menguy, University of Kentucky, Lexington, Ky.

"Gastrin and the Control of its Release" - David State, Albert Einstein College of Medicine, New York, N. Y.

"Vagal Influences in Gastric Secretion" - Daniel Shapira, Albert Einstein College of Medicine, New York, N. Y.

"Occurrence of Plasma Proteins in Gastric Mucus and Other Secretions" - Martin Horowitz, and Franklin Hollander, Mt. Sinai Hospital, New York, N. Y.

Session Chairman: Joseph B. Kirsner
University of Chicago, Chicago, Ill.

2:00 P.M.

"Recent Developments in Peptic Ulcer" - Joseph B. Kirsner, University of Chicago, Chicago, Ill.

"Certain Genetic Aspects of Peptic Ulcer, With Particular Reference to Blood Group" - Joseph A. Buckwalter, State University of Iowa, Iowa City, Iowa

"The Gastric Ulcer Problem" - Gordon McHardy, Louisiana State University School of Medicine, New Orleans, La.

"The Medical Management of Duodenal Ulcer" - David C. H. Sun, Mt. Alto Veterans Administration Hospital, Washington, D. C.

"Complications of Peptic Ulcer and Their Management" - William A. Haubrich, Henry Ford Hospital, Detroit, Mich.

PANEL DISCUSSION: "Pertinent Issues on Peptic Ulcer Disease"
Moderator, Joseph B. Kirsner, University of Chicago, Chicago, Ill.

TUESDAY, OCTOBER 17, 1961

Session Chairman: David C. H. Sun
Mt. Alto Veterans Administration Hospital and
The George Washington University
Washington, D. C.

9:00 A.M. –

"Pharmacodynamic Evaluation of Glycopyrrolate in Animals" - John W. Ward, B. V. Franko, R. S. Alphin and C. D. Lunsford, A. H. Robins Company, Inc., Richmond, Va.

"Clinical Evaluation of Promandeline 263" - Joseph M. Gambescia, Hahnemann Medical College and Hospital, Philadelphia, Pa.

"Comparative Pharmacological and Physiological Effects of Glycopyrrolate and Propantheline" - David C. H. Sun, Mt. Alto Veterans Administration Hospital, Washington, D. C.

"Physiological Effect and Clinical Evaluation of Glycopyrrolate in Peptic Ulcer Disease" - Hugo C. Moeller, University of California, San Francisco, Calif.

"Physiological and Clinical Evaluation of Gastric Acidity with Glycopyrrolate, Histamine, and Insulin Stimulation" - W. E. Abbott, Harvey Kriegler, and Alfy Sourial, University Hospitals of Cleveland, Cleveland, Ohio

"Action of Glycopyrrolate on Gastrointestinal Motility" - Robert Young, Georgetown University School of Medicine, Washington, D. C.

"The Role of Anticholinergic Drugs in the Treatment of Peptic Ulcer Disease" - Julian Ruffin and David Cayer, Duke University School of Medicine, Durham, N. C.

PANEL DISCUSSION

PRESENT STATUS OF VAGOTOMY: PHYSIOLOGIC AND CLINICAL ASPECTS

Session Chairman: Henry L. Bockus
Graduate School of Medicine
University of Pennsylvania, Philadelphia, Pa.

2:00 P.M. —
"Vagotomy" - Lester R. Dragstedt, Department of Surgery, University of Florida, Gainesville, Fla.

"Vagotomy and Pyloroplasty" - Stanley D. Hoerr, Cleveland Clinic, Cleveland, Ohio

"Vagotomy and Antrectomy" - H. William Scott, Department of Surgery, Vanderbilt University School of Medicine, Nashville, Tenn.

"Postvagotomy - Gastric Stasis" - James L. A. Roth, Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pa.

"Postvagotomy and Gastrectomy - Nutrition and Steatorrhea" - Perry J. Culver, Harvard Medical School, Boston, Mass.

PANEL DISCUSSION: *Moderator,* Henry L. Bockus, Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pa.

SECTION OF BIOLOGICAL AND MEDICAL SCIENCES

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NEW MEMBERS

Elected June 22, 1961

LIFE

Fujisaki, Charles K., M.D., Medicine. Physician and Surgeon, Mercy Hospital, Denver, Colo.

Haeff, Andrew V., Ph.D., Physics. Vice-President, Hughes Aircraft Co., Malibu, Calif.

Kerby, Grace P., M.D., Medicine. Professor of Medicine, Duke University, Durham, N. C.

SUSTAINING

Hartmann, Philippine, M.D., Cancer. Gynecologist, Private Practice Munich, Germany.

Paule, James Mitchel, M.D., Internal Medicine. Resident in Internal Medicine, V. A. Hospital, Dallas, Texas.

ACTIVE

Anderson, Albert Louis, M.D., Medical. Surgeon, Private Practice, Annapolis, Md.

Anduze, Roy A., M.D., General Surgery. Director, Knud-Hansen Memorial Hospital, Charlotte Amalie, St. Thomas, Virgin Islands.

Ashikawa, James K., Ph.D., Nuclear Medicine. Radiation Physicist, Los Angeles County Hospital, Los Angeles, Calif.

Baker, Frances Ellen, Ph.D., Mathematics. Professor of Mathematics, Vassar College, Poughkeepsie, N. Y.

Baker, Walter L., M.S., Acoustics. Assistant Professor, Pennsylvania State University, State College, Pa.

Baron, Frank J., Ph.D., Plant Physiology. Research Forester, U. S. Forest Service, Berkeley, Calif.

Barr, Lloyd, Ph.D., Muscle Physiology. Assistant Professor of Physiology, University of Michigan, Ann Arbor, Mich.

Bearman, Jacob E., Ph.D., Statistical and Mathematical Methods, in Medical and Public Health Research. Professor and Head, Division of Biostatistics, University of Minnesota, Minneapolis, Minn.

Becker, Bernard A., M.S., Pharmacology. Senior Research Pharmacologist, Strasenburgh Laboratories, Rochester, N. Y.

Bercovitz, Joseph, LL.B., Engineering. Patent Attorney, New York, N. Y.

Bester, Alfred, A.B., Microbiology. Author, *Holiday* Magazine, New York, N. Y.

Blackmore, William Russell, Ph.D., Physical Sciences. Operations Research Scientist, Canadian Industries Ltd., McMasterville, Que., Canada.

Brookes, Victor Jack, Ph.D., Insect Biochemistry. Assistant Professor, Oregon State University, Corvallis, Ore.

Brooks, Betty Watt, Ph.D., Public Health. Research Analyst, U. S. Public Health Service, Washington, D. C.

Burch, Neil Robinson, M.D., Psychiatric Research. Associate Professor of Psychiatry, Baylor University, Houston, Texas.

Carnahan, Robert E., Ph.D., Biological and Medical Sciences. Patent Agent, Mead Johnson Research Center, Evansville, Ind.

Caughey, Winslow Spaulding, Ph.D., Biochemistry. Assistant Professor Physiological Chemistry, Johns Hopkins University, Baltimore, Md.

Cesaro, Richard S., B.S., Astronautics. Vice-President, Corporate Planning Research and Development, Sands Point, N. Y.

Chao, Tsai H., Ph.D., Organic Chemistry. Senior Research Chemist, American Cyanamid Co., Somerville, N. J.

Daen, Jerome, Ph.D., Physical Chemistry. Assistant Professor of Chemistry, Lehigh University, Bethlehem, Pa.

Dan, Katsuma, Ph.D., Embryology. Professor of Embryology, Tokyo Metropolitan University, Tokyo, Japan.

Daudel, Raymond, D.Sc., Applied Waves Mechanics. Professor, Sorbonne, Paris, France.

Davis, R. F., Ph.D., Animal Nutrition. Professor and Head, Department of Dairy Science, University of Maryland, College Park, Md.

Djavaheri, Amir Assad, M.D., Surgery. Senior resident, Staten Island Hospital, Staten Island, N. Y.

Dunn, Robert George, Jr., M.D., Radiology. Director, Department of Radiology, Phoebe Putney Memorial Hospital, Albany, Ga.

Dyer, Denzel L., Ph.D., Biochemistry. Space Biotechnology Section, The Martin Co., Denver, Colo.

Eagle, Harry, M.D., Cell Biology. Chairman, Department of Cell Biology, Albert Einstein College of Medicine, New York, N. Y.

Evans, Evan C., III, A.B., Biophysics. U. S. Naval Radiation Defense Laboratory, Berkeley, Calif.

Ewing, Galen W., Ph.D., Chemical Instrumentation for Analysis. Professor of Chemistry and Acting Head of the Department, New Mexico Highlands University, Las Vegas, N. Mex.

Fabrizio, David P. A., B.A., Genetics. Research Assistant, South Jersey Medical Research Foundation, Camden, N. J.

Feinberg, Irwin, M.D., Clinical and Experimental Psychiatry. Acting Chief, Section of Psychopathology, National Institute of Mental Health, Bethesda, Md.

Feinstein, Donald, M.D., Internal Medicine. Resident in Internal Medicine, Los Angeles County General Hospital, Los Angeles, Calif.

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Elected September 21, 1961

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